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Development of New Transition Metal Catalyzed C-C Bond Forming Reactions and their Application toward Natural Product Synthesis

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Development of New Transition Metal Catalyzed C-C Bond Forming Reactions and their Application toward Natural Product Synthesis

by

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Dedication

To my hardworking teachers and loving parents.

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I am thankful to many people who have made it possible and easier for me to get Ph. D. degree. First of all, my father whose constant encouragement and love for knowledge seeking made it so much easier for me to concentrate on my studies. Beside of his average income he never hesitated to provide me with learning opportunity. I am grateful to my mother love, without I would never had been able to live the

I am grateful to my supervisor Prof. Michael J. Krische, for his endless support and endearing love for science influence not only my learning ability but improved my personality. Mike provided me with the ability to question any facts and findings, and increase my curiosity for science. He mentors my progress as a concerned friend and always provided with honest advice. He is my role model and it is a blessing to work with him. I wish him every success in life and happy and healthy life ahead.

I am also thankful to my teachers who always guided my in the right direction. I am blessed to have such a loving family. I must thank my brother Hammad Hassan, who always been a step ahead of me and provide me with a healthy competition growing up. I love my sisters and wish them a successful life.

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Development of New Transition Metal Catalyzed C-C Bond Forming Reactions and their Application toward Natural Product Synthesis

Abbas Hassan, Ph. D.

The University of Texas at Austin, 2011

Supervisor: Michael J. Krische

In Michael J. Krische research group we are developing new transition metal catalyzed Carbon-Carbon (C-C) forming reactions focusing on atom economy and byproduct free, environmental friendly approaches. We have developed a broad family of C-C bond forming hydrogenations with relative and absolute stereocontrol which provide an alternative to stoichiometric organometallic reagents in certain carbonyl and imine additions. Inspiring from the group work my goal was to develop new reactions, extend the scope of our group chemistry and their application towards synthesis of biologically active natural products. I have been part of enantioselective Rh catalyzed Aldol reaction of vinyl ketones to different aldehydes. Also, we have found that iridium catalyzed transfer hydrogenation of allylic acetates in the presence of aldehydes or alcohols results in highly enantioselective carbonyl allylation under the conditions of transfer hydrogenative. Based on this reactivity a concise enantio- and diastereoselective synthesis of 1,3-polyols was achieved *via* iterative chain elongation and bidirectional iterative asymmetric allylation was performed, which enables the rapid assembly of 1,3-polyol substructures with exceptional levels of stereocontrol. The utility of this approach stems from the ability to avoid the use of chirally modified allylmetal reagents, which require multistep preparation, and the ability to perform chain elongation directly from the alcohol oxidation level. This approach was utilized for the total synthesis of (+)-

Roxaticin from 1,3-propanediol in 20 longest linear steps and a total number of 29 manipulations. Further, advancements were made in iridium catalyzed C-C bond formation under transfer hydrogenation. While methallyl acetate does not serve as an efficient allyl donor, the use of more reactive leaving group in methallyl chloride compensate for the shorter lifetime of the more highly substituted olefin π-complex. Based on this insight into the requirements of the catalytic process, highly enantioselective Grignard-Nozaki-Hiyama methallylation is achieved from the alcohol or aldehyde oxidation levels. Also, a catalytic method for enantioselective vinylogous Reformatsky- type aldol addition was developed in which asymmetric carbonyl addition occurs with equal facility from the alcohol or aldehyde oxidation level. Good to excellent levels of regioselectivity and uniformly high levels of enantioselectivity were observed across a range of alcohols and aldehydes.

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1.1 Introduction

Polyketide natural products are one of the most complex groups of secondary metabolite originates from plants, animals, fungi and bacteria. The common feature of this class is they are biosynthesis product of enzymes polyketide syntheses (PKS), by recurring linear addition of two or three carbons building blocks named as polyacetates or polypropionates.[1] This apparently simple two or three carbon chain elongation can give rise to complex families of compounds such as polyenes, polyphenols, polyethers and macrolides. Nearly 10,000 members of this class have been characterized exhibiting complex structural features.[1e] Like other secondary metabolites their exact role in biological systems is not known, it is believed that they can function as pigments, virulence factors, infochemicals, or for defense. However, from a human pharmacological point of view, polyketides displays extensive practice in human medicine. Polyketide natural products possess antibiotic, anticancer, antiparasitic, antifungal and immunosuppressive properties.[2] Approximately 20% of the top-selling small molecule drugs are polyketides, and it is estimated that polyketides are five times more likely to possess drug activity compared to other natural product families (Figure 1.1).

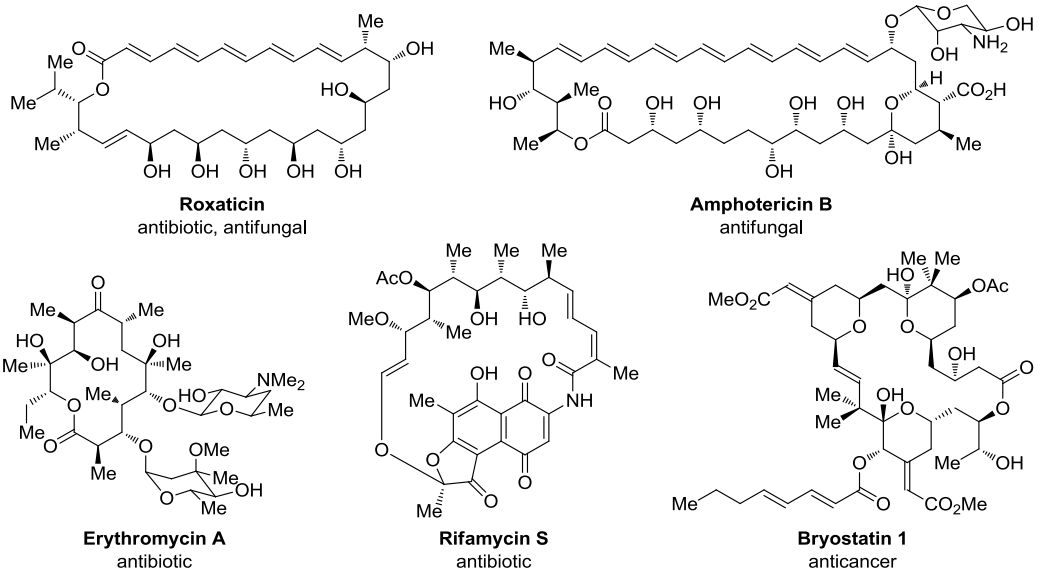


Figure 1.1 Example of polyketide natural products.

The polyketide biosynthesis is extensively reviewed, particularly a comprehensive survey in 2001 by Stasunton.[1f] Here we will refresh our memory how different oxidation level in complex polyketide natural product are achieved. Later we will discuss efforts from our laboratory for the synthesis of polyketide natural products.

1.2 Polyketide Biosynthesis

As investigations into polyketide biosynthesis[1] and chemical biology continue to uncover important biological pathways and novel therapeutic targets, the design of synthetic[3] and bio-engineered[4] methods for polyketide construction remains at the forefront of research. It is very important from synthetic chemist point of view to understand the polyketide biosynthesis parting into different redox state and complex template, so that can be mimicked or replaced in laboratory. In recent years, lots of efforts have been put forth in chemical synthesis mimicking polyketide biosynthesis.

Polyketide biosynthesis is principally similar to fatty acid biosynthesis, as both follow similar mechanism of iterative chain elongation employing common building blocks such as, acetyl coenzyme A (CoA) and malonyl-CoA (MCoA) units. The multifunctional enzyme complexes, polyketide synthesas (PKSs) are responsible for such iterative addition sequence. The polyketide synthesis initiate by a decarboxylative Claisen condensation of an acyl transfer unit attached to an acyl carrier protein (ACP) with malonyl-CoA, mediated by ketosynthase (KS). The ACP is a phosphopantetheine acyl carrier protein, attached to extending chain by a thiol residue, function as a long flexible arm transports the growing chain to various enzymes required for chain extension. The condensation product is a β-keto ester, which can repeat the same process as required adding two or more carbon unit to the growing chain giving rise to polyketide, having a carbonyl group at alternate position along the chain. These polyketides generally cyclizes to aromatic intermediates, which in turn evolves in polyphenolic among other natural products.

However, the PKSs can differentiate the β-keto ester in a highly selective and control manner to generate polyketides in reduced oxidation states. Such as, the β-keto ester is reduced by a ketroreductase (KR) to generate β-hydroxy ester. Further dehydration by dehydratase (DH)

will introduce unsaturation and finally again reduction by enoyl reductase (ER) will produce saturated polyketide subunits. These differentiation processes can be intercepted at any stage to an acyl transfer process to generate a different ketosynthase (KS), enable it to re-enter the biosynthesis (Figure 1.2).

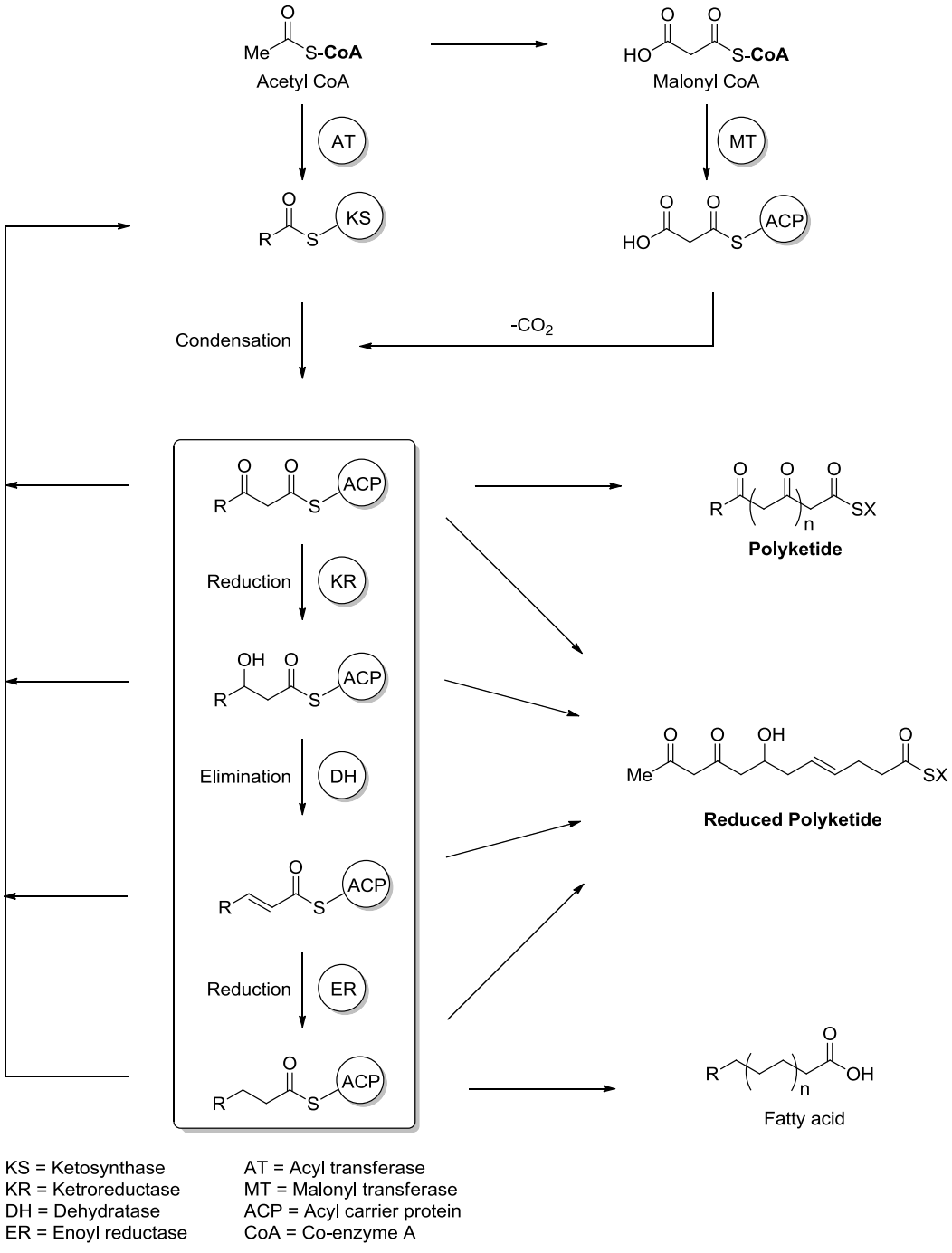
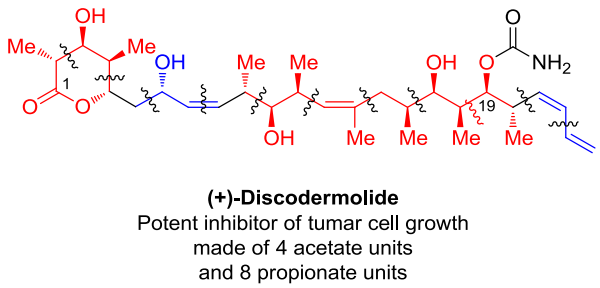


Figure 1.2 Schematic representation of Polyketide synthesis.

PKSs assemble the polyketide intermediates in a highly selective and controlled manner in different oxidation level, such as these differentiations can give rise to ketone, hydroxyl, olefin and deoxygenative polyacetates and polypropionates as evidently observe in many complex natural products. In divergence to polyketide, fatty acid biosynthesis follows the full cycle of reduction to give rise to fatty acids. The initial polyketide chain formed may survive in some cases, but mostly it is further elaborated by addition biosynthetic modification to give structurally more complex products. Examples of these elaboration processes are oxidative changes, for instance hydroxylation, epoxidation, oxidative cleavage, alkylation, esterification and glycosylation. These permutations of chain assembly and elaboration result in great diversity in polyketide structures. Indeed the biosynthesis is programmed in genetic codes, until recently considerable understandings have been made. Discodermolide an anticancer polyketide for example is made up of four acetate and 8 propionate units. It also has a 6-membered lactone at C-1 and *O*-amide at C-19 (Figure 1.3).



(+)-Discodermolide
Potent inhibitor of tumar cell growth
made of 4 acetate units
and 8 propionate units

Figure 1.3 Discodermolide, showing the acetate (blue) and propionate (red) units.

1.3 Polyketide Chemical Synthesis

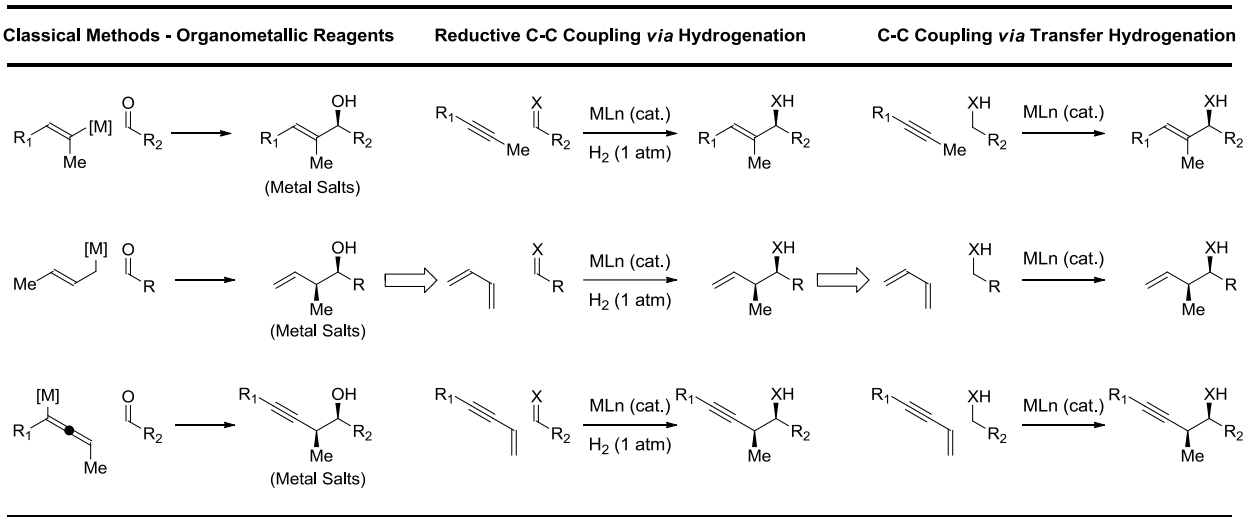
In general, the low natural abundance of polyketide natural products and tedious isolation protocols coupled with biomimetic approaches are in infancy, required efficient chemical synthesis.[3] However, these devoted and meticulous efforts are still very compelling, challenging, unviable, strenuous and above all low yielding. A convincing case is the Novartis synthesis of discodermolide, enabling availability for clinical trial in anticancer study. As the biosynthesis of polyketide started with recurring addition of small structural unit to make complex natural product, it would be highly desirable if we can learn from nature and can apply the same approach to chemical synthesis of polyketide. This strategy however, is challenging to imitate in

chemical synthesis, since the length of the resulting synthetic scheme quickly becomes intractable. The problem on hand is by far that simple, chemical reactivity, regioselectivity and stereoselectivity coupled with the backbone modifications are difficult as well. There are many methods for complex molecule exists, yet the majority of this technology required the use of multi-stage preactivation, premetallated nucleophiles, chiral auxiliaries, chiral reagents and excessive byproduct generation.

1.4 Hydrogenation and Transfer Hydrogenation C-C Bond Formation

Many methods for complex molecule synthesis exist, yet the majority of this technology is not easily brought to scale. Hence, there is an authentic need to discover and develop catalytic processes that embody the principal characteristics of "process-relevance," in particular, the ability to transform abundant, renewable feedstocks to value-added products in the absence of stoichiometric byproducts. This quality is embodied by catalytic hydrogenation, which has found broad application across all segments of the chemical industry, including the manufacture of chiral pharmaceutical ingredients, and alkene hydroformylation[5], the prototypical C-C bond forming hydrogenation and largest volume application of homogenous catalysis.[6, 7] Inspired by the impact of hydrogenation and hydroformylation, we have developed a broad, new family of eanantioselective C-C bond forming hydrogenation and transfer hydrogenations. The atom-economy exhibited by these transformations, particularly the exclusion of stoichiometric metallic byproducts, suggests these methods would be viable candidates for use at the process level upon minimization of catalyst loading.

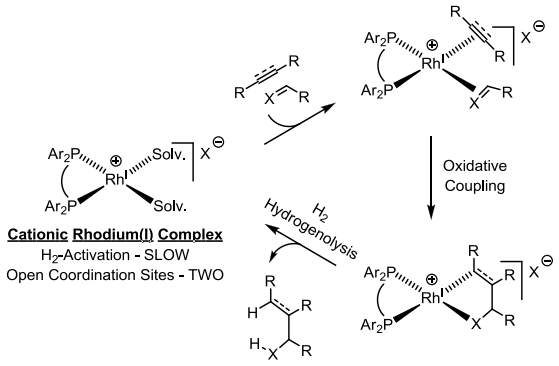
We have found that diverse π-unsaturated reactants are reductively coupled to polarized C=X (X = O, NR) bonds under hydrogenation conditions, offering an alternative to stoichiometric organometallic reagents in a broad range of carbonyl and imine addition processes. This concept is extended further by related transfer hydrogenative processes, for which hydrogen exchange between alcohols and π-unsaturated reactants triggers generation of electrophile-nucleophile pairs that combine to form products of carbonyl addition directly from the alcohol oxidation level (Scheme 1.1).[8]



Scheme 1.1 Hydrogen-mediated C=X (X = O, NR) addition bypasses stoichiometric byproduct generation.

1.4.1 C-C Bond Forming Hydrogenation

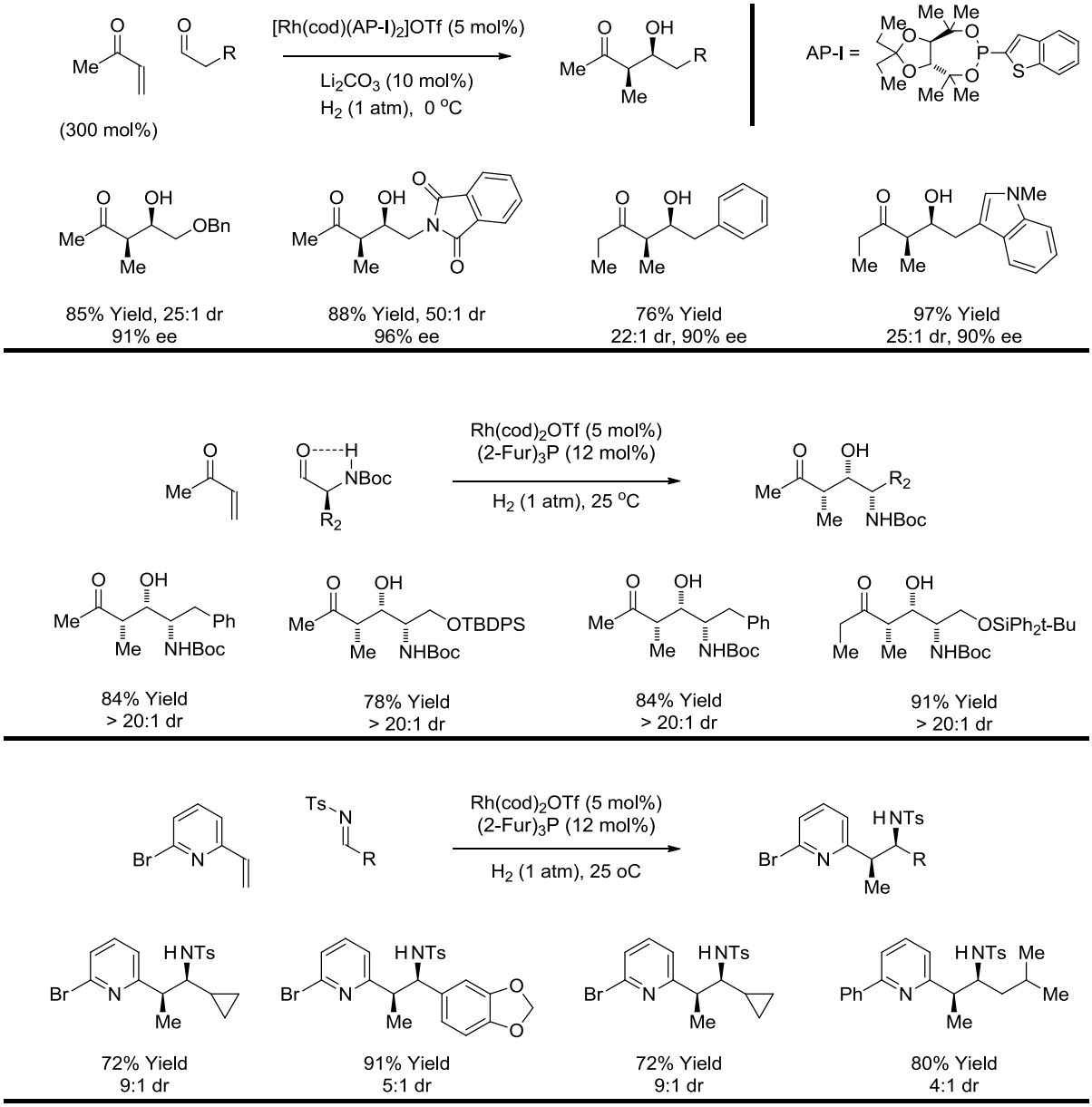
Despite its routine use for well over a century, alkene hydroformylation and the parent Fischer-Tropsch process were the only examples of hydrogen-mediated reductive coupling at the onset of our studies.4-6 Hence, it became necessary to identify a mechanistic pathway that would unlock hydrogenation for C-C bond formation. Whereas neutral rhodium complexes engage in rapid hydrogen oxidative addition,[9] hydrogen oxidative addition is turnover limiting for cationic rhodium catalysts.[10,11] Accordingly, for cationic complexes of rhodium, it was found that the diminished rate of hydrogen oxidative addition, along with the availability of an additional coordination site, conspire to promote oxidative coupling to form metallacyclic intermediates, which participate in hydrogenolysis to form products of reductive C-C bond formation in the absence of byproducts (Scheme 1.2).



Scheme 1.2 Cationic rhodium complexes promote hydrogen-mediated reductive coupling *via* oxidative coupling pathways.

Through the implementation of oxidative coupling pathways, numerous C-C bond forming hydrogenations were developed. For example, hydrogenation of enones in the presence of aldehydes employing a cationic rhodium catalyst modified by a TADDOL-like phosphonite ligand delivers products of reductive aldol addition with high levels of relative and absolute stereocontrol.[12] The aldol reaction is one of the most important transformations for the synthesis of polyketide as it follows the same technique for C-C bond as utilized in biosynthesis as Claisen condensation. There has been tremendous amount of work done in this field. The important feature is the synthesis of branch selective aldol addition as lacking in unsymmetrical ketone, aldehyde organocatalysis.

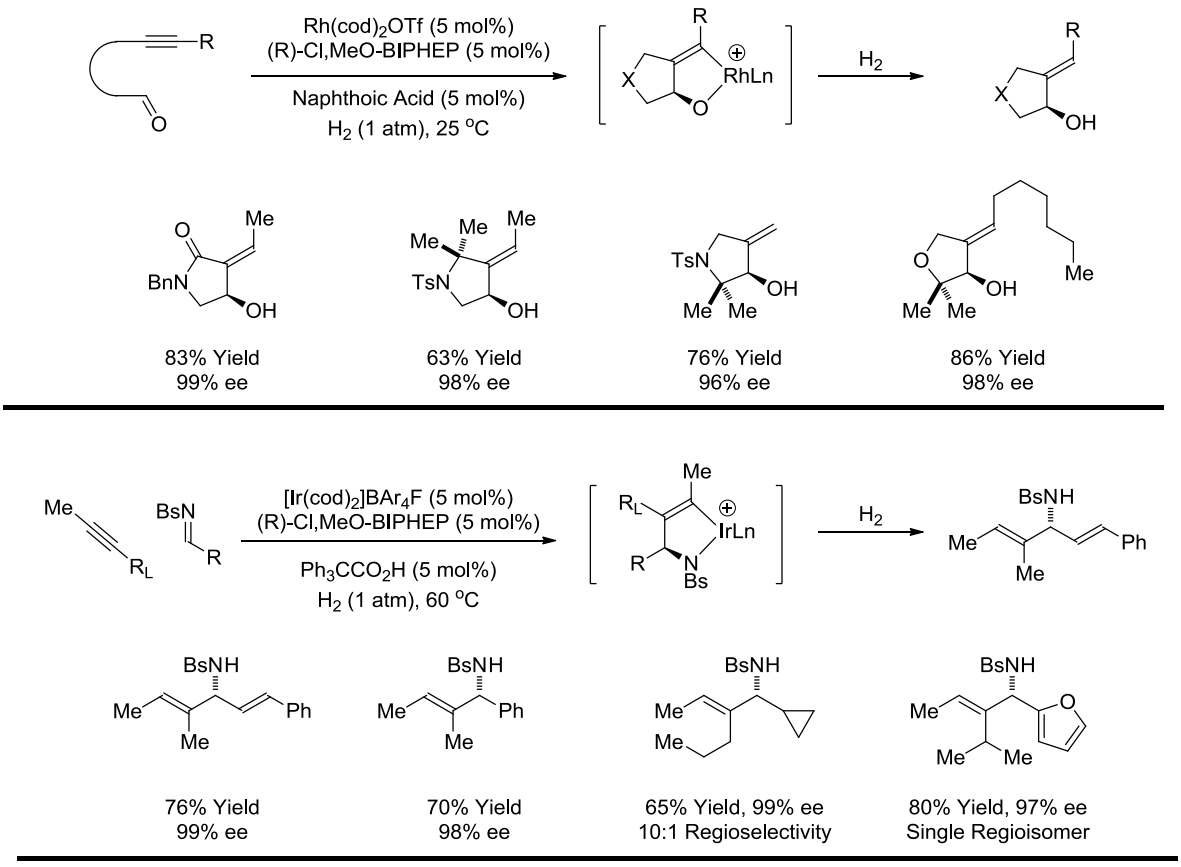
Similarly, high levels of substrate directed asymmetric induction are achieved in hydrogen-mediated reductive aldol additions to *N*-Boc-α-amino aldehydes.[13] Notably, due to their configurational instability of *N*-Boc-α-amino aldehydes, corresponding additions of alkali enolates are unknown. This reactivity pattern is applicable to related activated olefins, as demonstrated by hydrogen-mediated coupling of 2-vinylpyridines and *N*-arylsulfonyl imines to furnish branched products of imine addition.[14] In each case, *syn*-diastereoselectivity is observed, as the adjacent substituents about the metallacyclic intermediate prefer a *trans*-orientation (Scheme 1.3).



Scheme 1.3 Hydrogenation of activated olefins to form products of C-C bond formation.

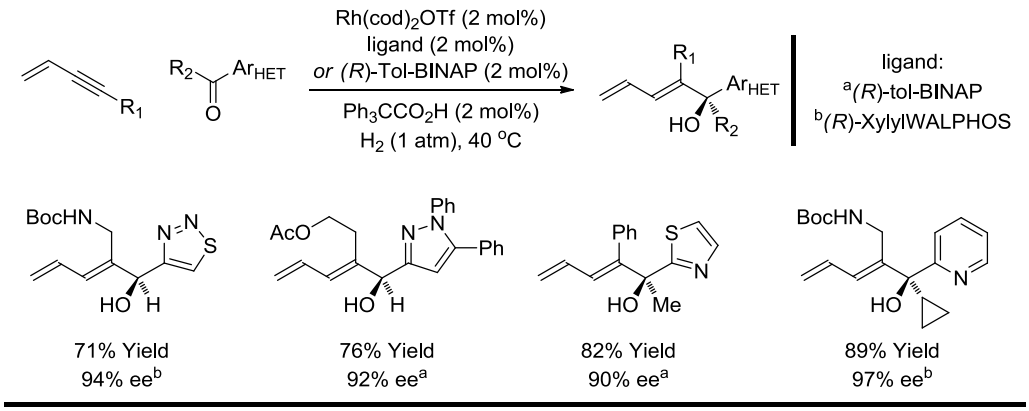
Next important reaction in polyketide synthesis is vinylation of carbonyls availing the same connectivity in variety of polyketide. Hydrogenation of alkynes in the presence of carbonyl and imine partners provides allylic alcohols and allylic amines, respectively, in the absence of stoichiometric byproducts. For example, hydrogenation of acetylenic aldehydes employing a cationic rhodium catalyst induces reductive cyclization to form enantiomerically enriched heterocycles.[15] Using cationic iridium catalysts, hydrogenation of 1,2-dialkyl substituted alkynes

in the presence of *N*-arylsulfonyl imines provides trisubstituted allylic amines.[16] For both processes, complete levels of *E*:*Z* selectivity (≥95:5) is observed. Such alkyne-C=X (X = O, NR) reductive couplings bypass use of preformed vinylmetal reagents (Scheme 1.4).



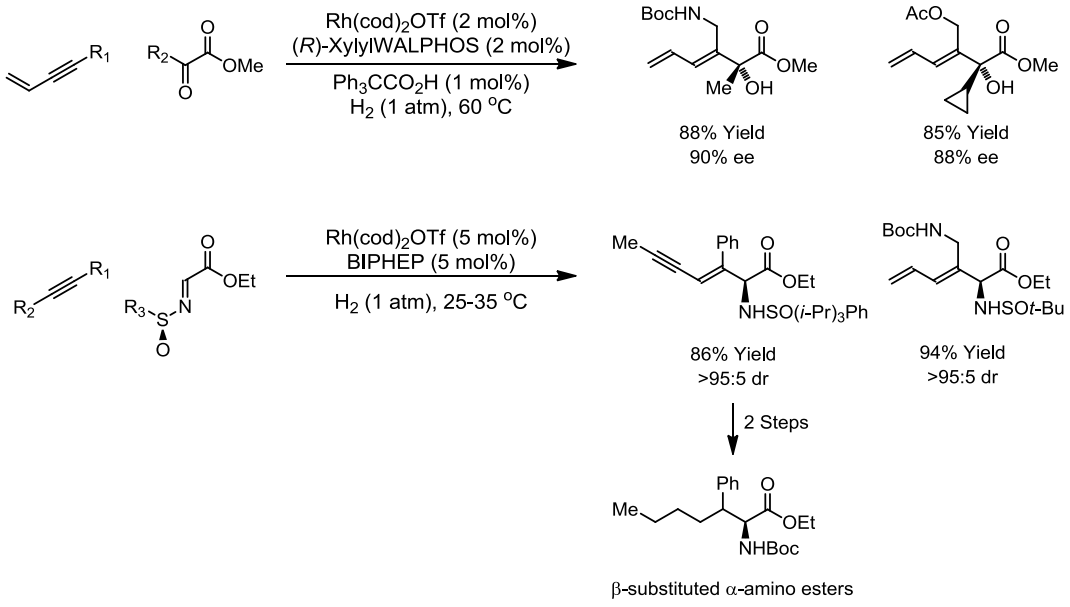
Scheme 1.4 Intra- and intermolecular hydrogen-mediated C-C coupling of unactivated alkynes.

Underscoring functional group compatibility, diverse heterocyclic aromatic aldehydes and ketones are subject to hydrogen-mediated reductive coupling to conjugated enynes to provide heteroaryl substituted secondary and tertiary carbinols, respectively. Using rhodium catalysts modified by (*R*)-tol-BINAP or (*R*)-xylyl-WALPHOS, uniformly high levels of enantioselectivity are observed. Manipulation of the diene moiety of the coupling products allows access to a variety of functional group arrays (Scheme 1.5).[17]



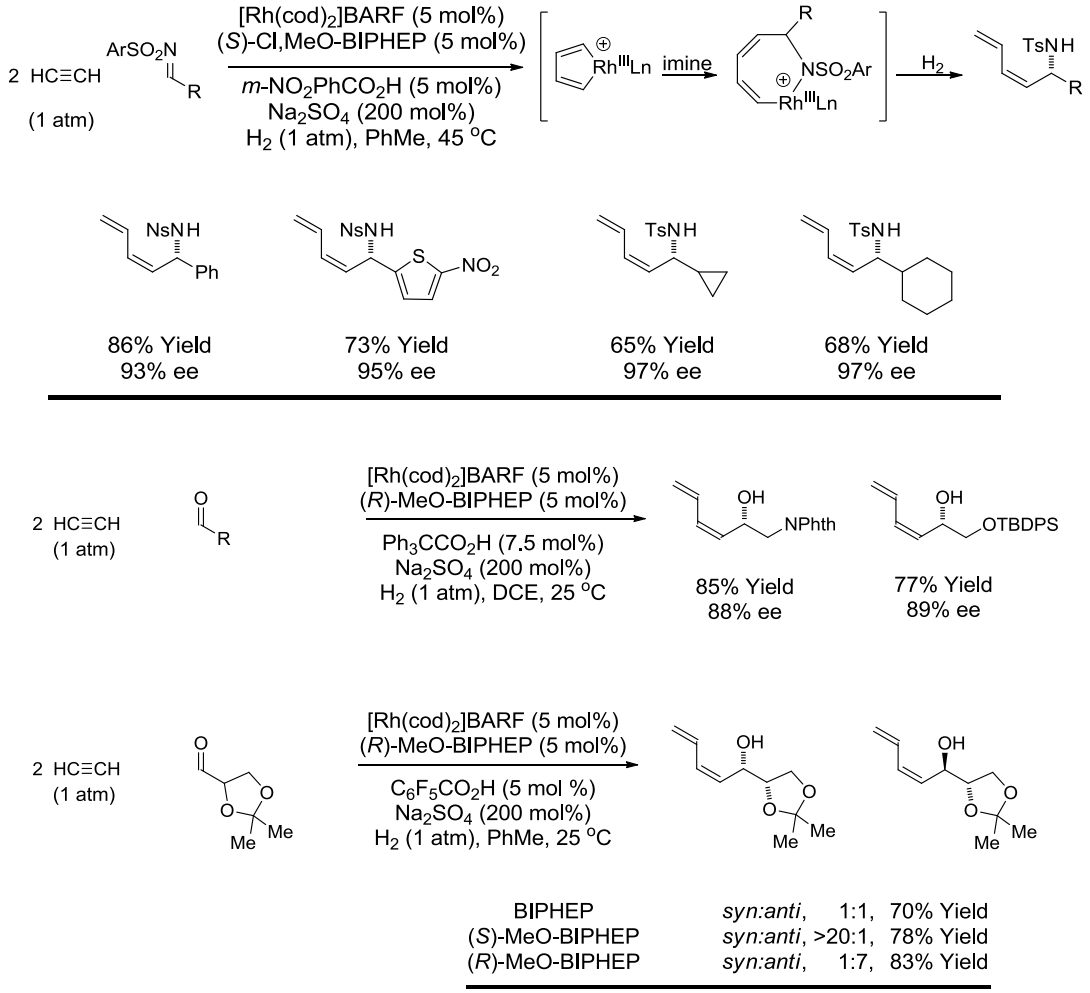
Scheme 1.5 Hydrogen-mediated couplings of 1,3-enynes with heterocyclic aromatic aldehydes or ketones.

Using cationic rhodium catalysts, hydrogenation of conjugated alkynes in the presence of glyoxalates and pyruvates provides the corresponding α-hydroxy esters with high levels of enantiomeric enrichment.[18] Conjugated enynes and diynes also participate in reductive couplings to (*N*-sulfinyl)iminoacetates under the conditions of rhodium catalyzed hydrogenation.[19] Using appropriately substituted *N*-sulfinyl substituent,[20] the corresponding β,γ-unsaturated α-amino acid esters are generated as single diastereomers. Exhaustive hydrogenation of the diene or enyne side chain of the C-C coupling product provides access to *β*-substituted α-amino acids (Scheme 1.6).



Scheme 1.6 Formation of α-hydroxy esters and α-amino esters via C-C bond forming hydrogenation.

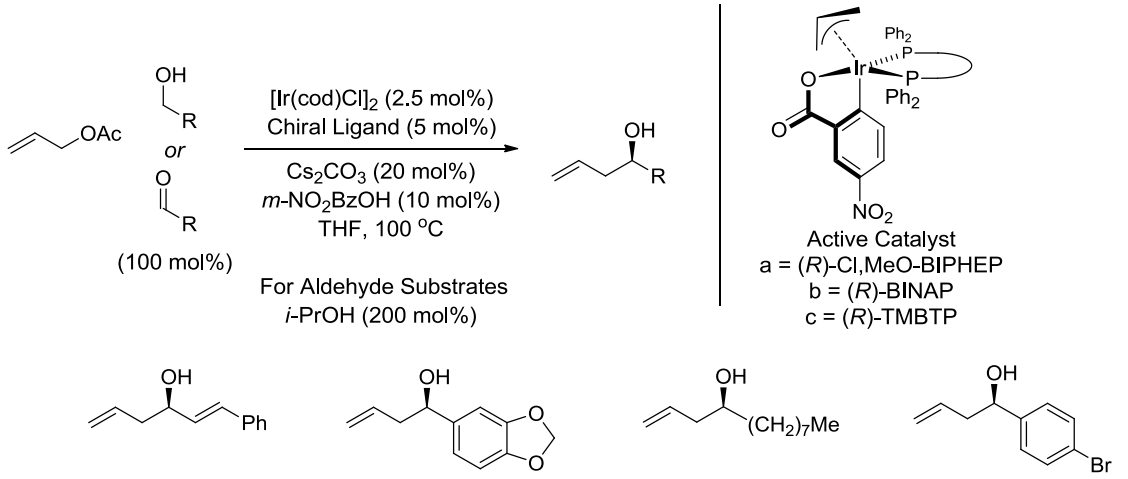
The hydrogen-mediated reductive coupling of acetylene in the presence of carbonyl and imine partners provides products of (*Z*)-butadienylation.[21] As corroborated by isotopic labeling, ESI-MS and computational studies,[22] the reaction occurs through an unusual mechanism involving formation of a rhodacyclopentadiene[23] followed by C=X (X = O, NR) insertion and hydrogenolysis of the seven-membered metallacycle. Using chirally modified cationic rhodium catalysts, allylic alcohols and allylic amines are formed in highly optically enriched form. Hydrogenative coupling of acetylene to α-chiral aldehydes using enantiomeric rhodium catalysts ligated by (*S*)-MeO-BIPHEP and (*R*)-MeO-BIPHEP provides adducts with good levels of catalyst directed diastereoselectivity. The latter process enabled a formal synthesis of all eight L-hexoses (Scheme 1.7).[23c]



Scheme 1.7 Rhodium catalyzed hydrogenation of acetylene in the presence of carbonyl and imine partners.

1.4.2 C-C Bond Forming Transfer Hydrogenation

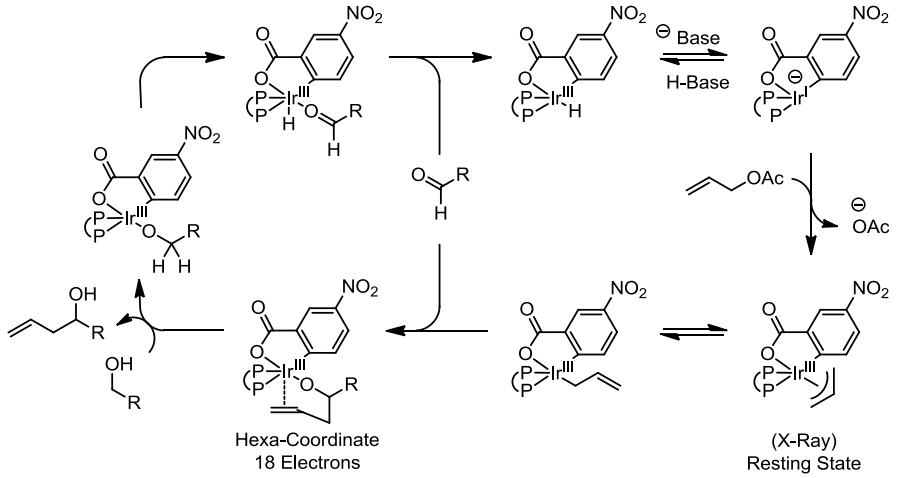
Under transfer hydrogenation conditions using *ortho*-cyclometallated iridium catalysts generated in situ from allyl acetate, 3-nitrobenzoic acid and a chiral *bis*-phosphine ligand, enantioselective carbonyl allylation is achieved from the alcohol or aldehyde oxidation level using allyl acetate as the allyl donor.[24] Aliphatic, allylic and benzylic alcohols are transformed to the corresponding homoallylic alcohols with uniformly high levels of enantioselectivity. In the presence of isopropanol, but under otherwise identical conditions, aldehydes are converted to an equivalent set of adducts. This protocol circumvents cryogenic conditions and the stoichiometric use of metallic reagents or reductants (Scheme 1.8).



Scheme 1.8 Enantioselective iridium catalyzed carbonyl allylation from the alcohol or aldehyde oxidation level

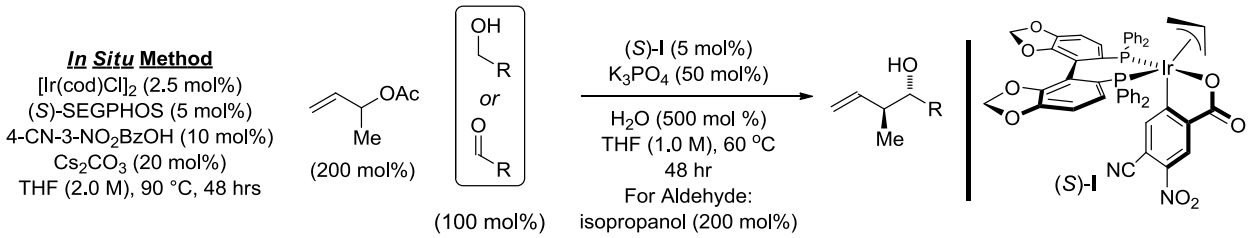
The cyclometallated iridium π-allyl *C,O*-benzoate complexes, which have been characterized by single crystal x-ray diffraction, are sufficiently robust that they may be purified chromatographically. A catalytic mechanism consistent with the collective data begins with protonolysis of the iridium π-allyl complex by the reactant alcohol to furnish a pentacoordinate iridium alkoxide. *β*-Hydride elimination produces aldehyde and an iridium hydride, which deprotonates to generate an anionic iridium(I) intermediate. Oxidative addition of allyl acetate provides the π-allyl complex. Because the π-allyl complex is the catalyst resting state, it can be

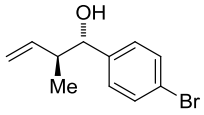
chromatographically recovered from the reaction mixture. Turnover-limiting aldehyde addition provides an iridium alkoxide. This hexacoordinate 18-electron complex is resistant to *β*-hydride elimination due to coordination of the homoallylic olefin. Exchange of the homoallylic iridium alkoxide with reactant alcohol releases the product and regenerates the pentacoordinate iridium alkoxide to close the catalytic cycle (Scheme 1.9).

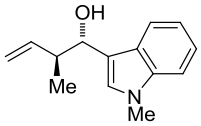


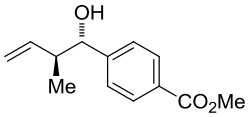
Scheme 1.9 Catalytic mechanism for iridium catalyzed carbonyl allylation under transfer hydrogenation conditions.

Corresponding carbonyl crotylations employing α-methyl allyl acetate can be conducted using the iridium *C,O*-benzoate complex that is assembled *in situ* from $[Ir(cod)Cl]_2$, allyl acetate, 4-cyano-3-nitrobenzoic acid and the chiral phosphine ligand (*S*)-SEGPHOS.[25a] However, although *in situ* assembly of the catalyst is convenient and excellent enantioselectivities typically were observed (>95% ee), only modest levels of *anti*-diastereoselectivity were evident (5:1 – 11:1 dr). Use of the chromatographically purified catalyst allows the reaction to be performed at lower temperature (60 ^{o}C), resulting in enhanced levels of *anti*-diastereo- and enantioselectivity (Scheme 1.10).[28b]

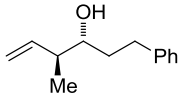


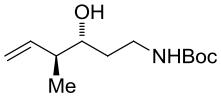


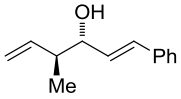




	Preformed (*S*)-**I**	Preformed (*S*)-**I**	Preformed (*S*)-**I**
Alcohol	78% Yield, 16:1 dr, 97% ee	75% Yield, 7:1 dr, 97% ee	78% Yield, 11:1 dr, 97% ee
Aldehyde	82% Yield, 17:1 dr, 98% ee	74% Yield, 10:1 dr, 98% ee	81% Yield, 13:1 dr, 98% ee
	In Situ (*S*)-**I**	*In Situ* (*S*)-**I**	*In Situ* (*S*)-**I**
Alcohol	73% Yield, 8:1 dr, 95% ee	73% Yield, 5:1 dr, 95% ee	70% Yield, 7:1 dr, 95% ee
Aldehyde	78% Yield, 11:1 dr, 97% ee	78% Yield, 6:1 dr, 97% ee	80% Yield, 11:1 dr, 96% ee







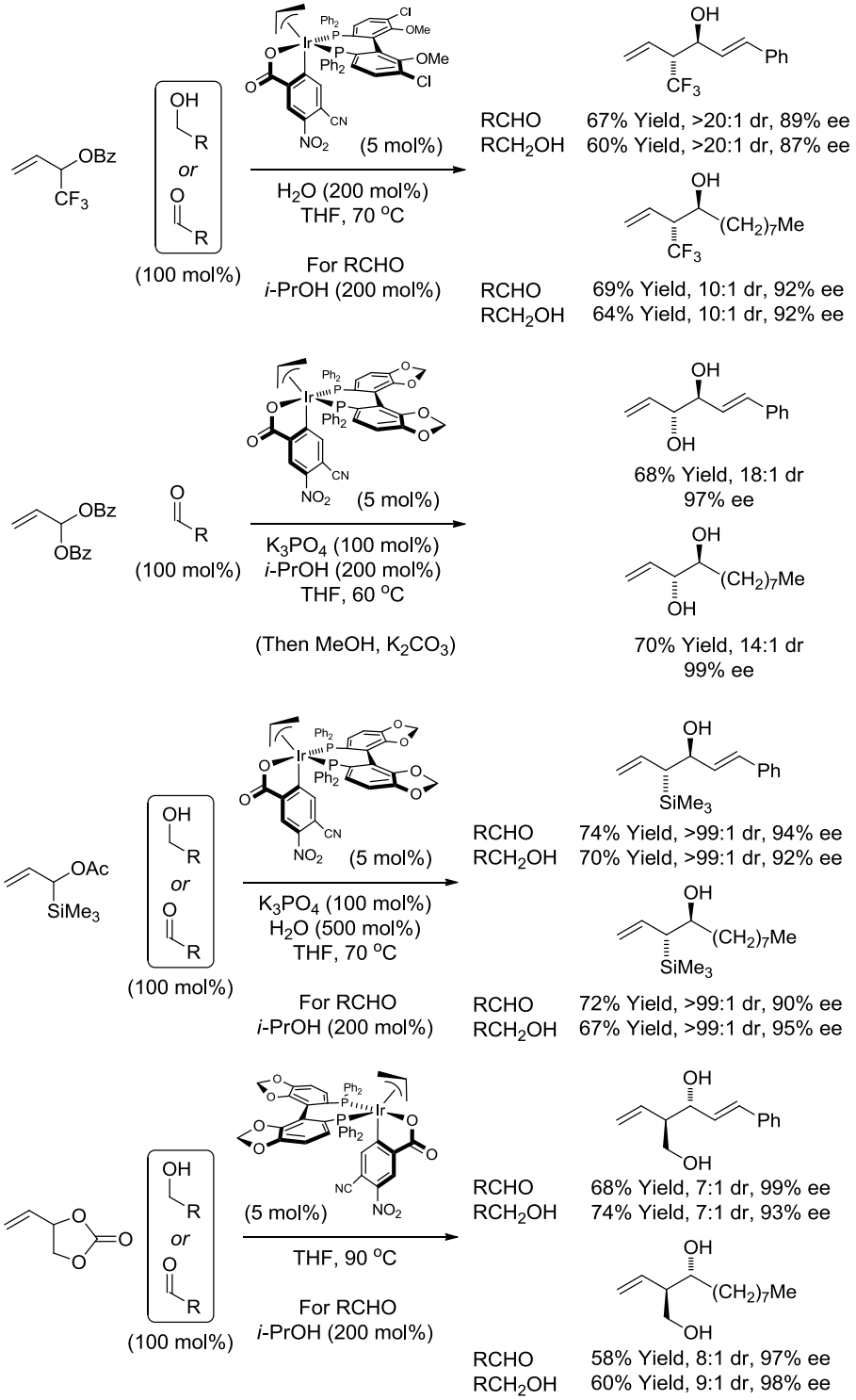
	Preformed (*S*)-**I**	Preformed (*S*)-**I**[b]	Preformed (*S*)-**I**
Alcohol	71% Yield, >20:1 dr, 99% ee	71% Yield, >20:1 dr, 96% ee	72% Yield, 10:1 dr, 93% ee
Aldehyde	71% Yield, >20:1 dr, 98% ee	66% Yield, >20:1 dr, 99% ee	77% Yield, 10:1 dr,98% ee
	In Situ (*S*)-**I**	*In Situ* (*S*)-**I**	*In Situ* (*S*)-**I**
Alcohol	69% Yield, 7:1 dr, 98% ee	no product observed	61% Yield, 7:1 dr, 86% ee
Aldehyde	71% Yield, 11:1 dr, 98% ee		66% Yield, 8:1 dr, 98% ee

Scheme 1.10 Enantioselective iridium catalyzed carbonyl crotylation from the alcohol or aldehyde oxidation level.

Enantioselective carbonyl allylation and crotylation from the alcohol oxidation level enables carbonyl allylation processes that are not possible using conventional allylmetal and crotylmetal reagents. For example, although 1,3-dialdehydes are intractable and cannot be used in enantioselective double allylation,[26] 1,3-propanediols are stable and engage in efficient two-directional allylation to provide C_2-symmetric adducts.[27] In these processes, the minor enantiomer of the *mono*-allylated intermediate is transformed to the *meso*-diastereoisomer, thus amplifying enantioselectivity.[28]

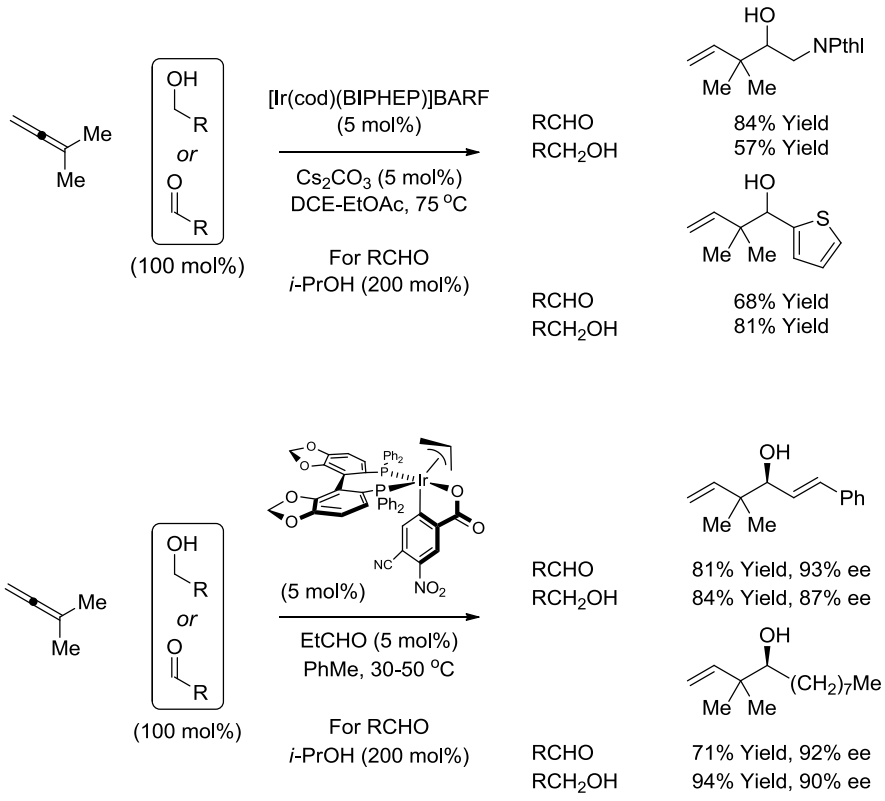
Beyond carbonyl allylation and crotylation, other types of enantioselective allylations are promoted by *ortho*-cyclometallated iridium catalysts, including α-(trimethylsilyl)allylation,29a α-(hydroxymethyl)allylation35b α-(trifluoromethyl)allylation[35c] and α-(hydroxy)allylation.[35d] In

each case, enantioselective carbonyl addition is achieved in the absence of stoichiometric metallic reagents (Scheme 1.11).



Scheme 1.11 Enantioselective double and polypropionate building blocks.

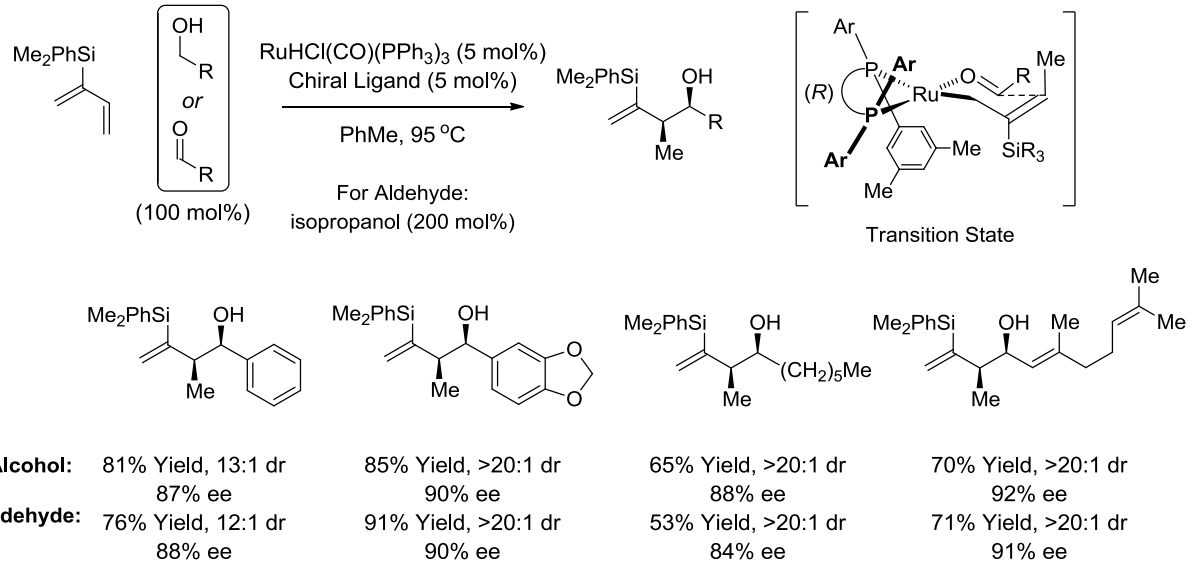
The appearance of iridium hydrides in the catalytic mechanism, suggests the feasibility of recruiting allenes and dienes as allyl donors *via* hydrometallation. Indeed, cyclometallated iridium *C,O*-benzoates modified by (S)-SEGPHOS promote enantioselective carbonyl *tert*-prenylation from the alcohol or aldehyde oxidation level under exceptionally mild conditions (30-50 ^{o}C).[30] For reactions conducted from the alcohol oxidation level, stoichiometric byproducts are completely absent. Interestingly, the absolute stereochemistry of *tert*-prenylation is opposite to that observed in the aforementioned allylations (Scheme 1.12).



Scheme 1.12 Enantioselective carbonyl *tert*-prenylation from the alcohol or aldehyde oxidation level.

Finally, transfer hydrogenation catalysts based on ruthenium also promote carbonyl addition from the alcohol or aldehyde oxidation level. For example, using chiral ruthenium catalysts modified by (*R*)-SEGPHOS or (*R*)-DM-SEGPHOS, the indicated silyl-substituted butadiene, which is prepared in a single manipulation from chloroprene, engages in *syn*-diastereo- and enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level.[31] Here, to address the issue of relative stereocontrol, the silyl-substituent directs formation

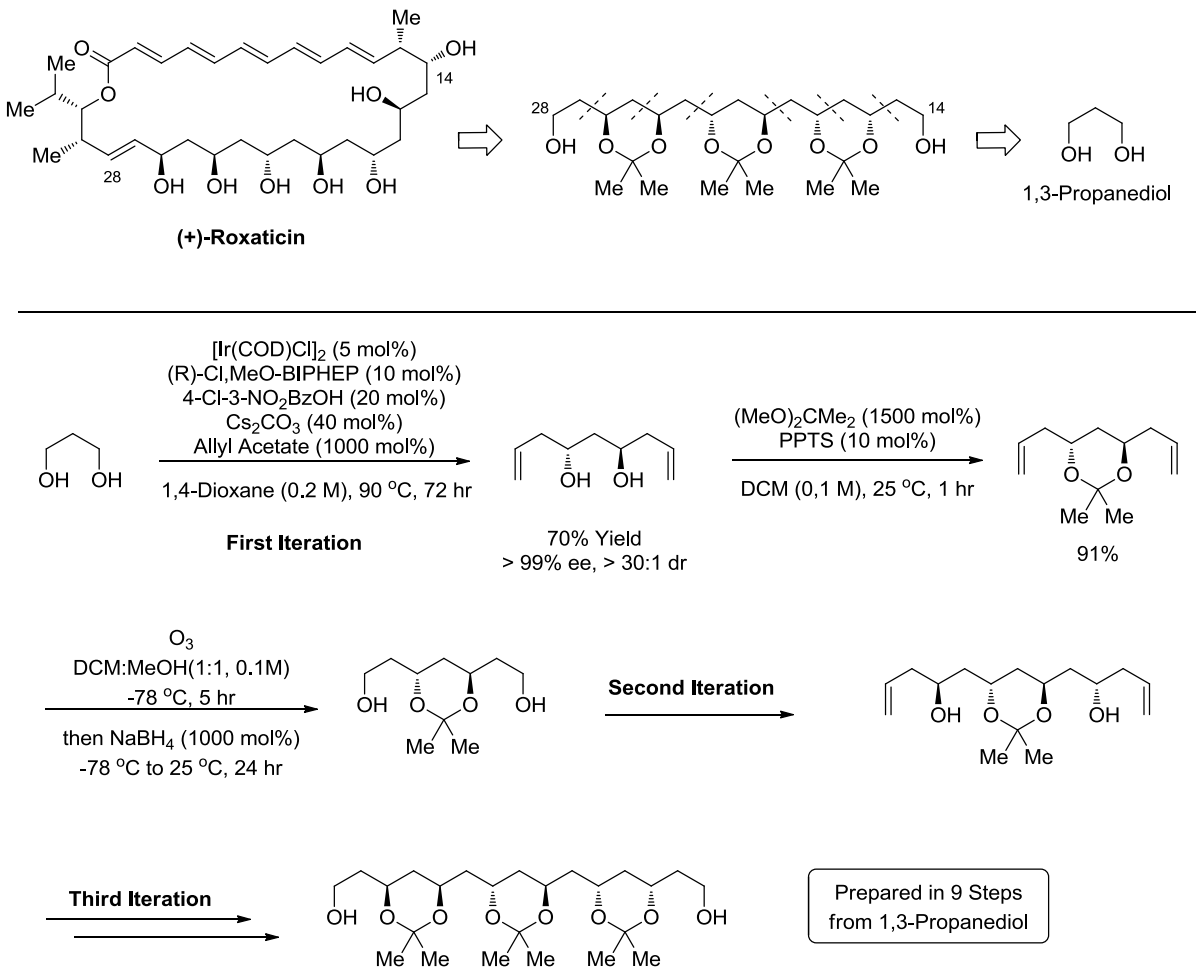
of geometrically defined σ-allylruthenium intermediates, which react stereospecifically through closed, chair-like transition structures (Scheme 1.13).



Scheme 1.13 Enantioselective *syn*-diastereo- and enantioselective carbonyl crotylation from the alcohol or aldehyde oxidation level *via* ruthenium catalyzed transfer hydrogenation.

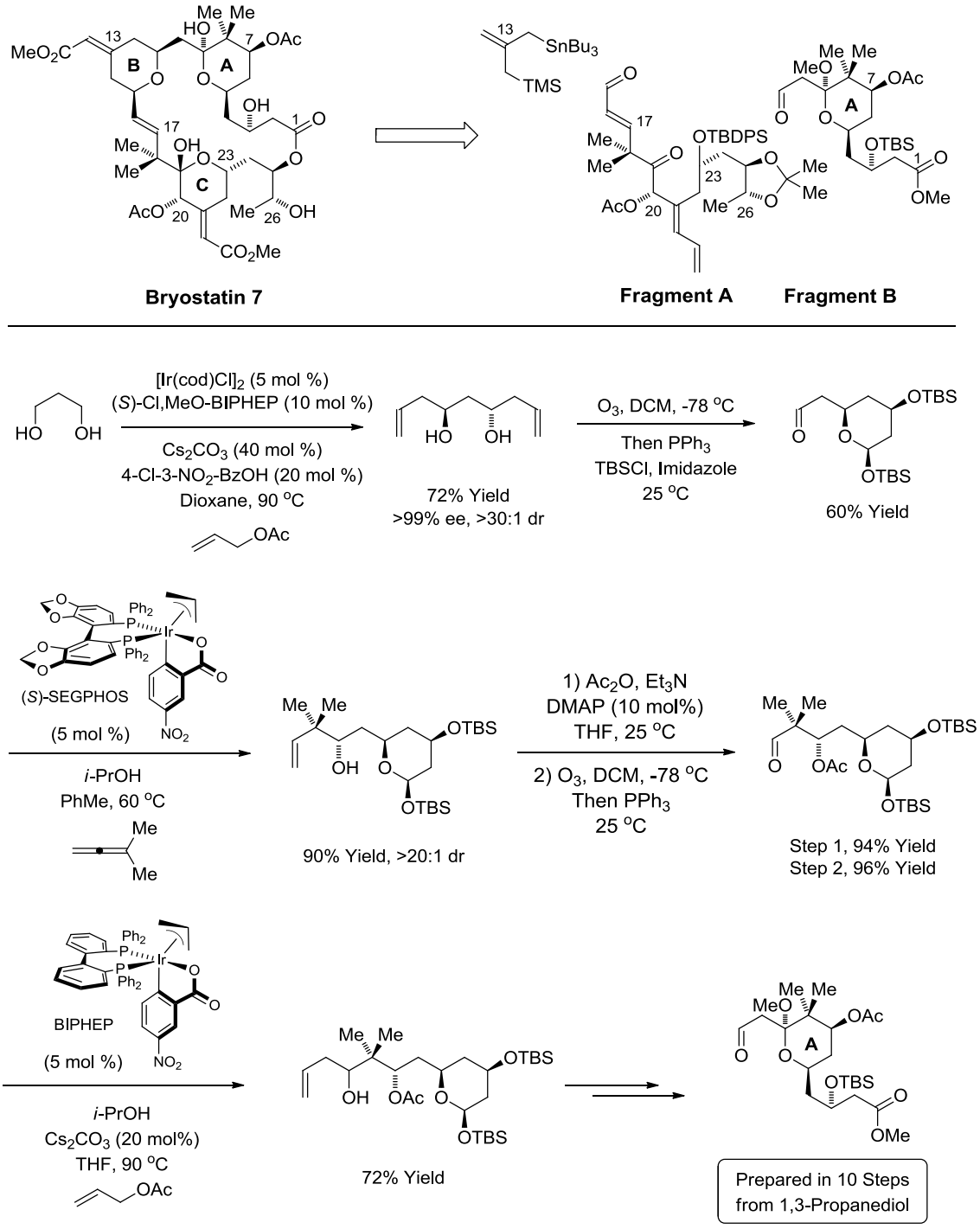
1.5 Application in Polyketide Synthesis

Through iterative two-directional chain elongation of 1,3-propanediol, a total synthesis of the oxo-polyene macrolide (+)-roxaticin was achieved in 20 steps.[32] Corresponding double crotylations of 2-methyl-1,3-propanediol result in the generation of *pseudo*-C_2-symmetric polypropionate stereoquintets the fragment C14−C28 which appear as substructures in diverse polyketide natural products. In this approach, nine of ten C-C bonds formed in the longest linear sequence was made *via* metal catalysis, including 7 C-C bonds formed *via* iridium catalyzed alcohol C-C coupling. The important feature of this approach bypasses the redox manipulations and use of any chiral auxiliary. Notably, this total synthesis represents the most concise preparation of any oxo-polyene macrolide reported to date, and is achieved in the absence of chiral reagents, chiral auxiliaries and with minimal use of premetallated *C*-nucleophiles (Scheme 1.14).



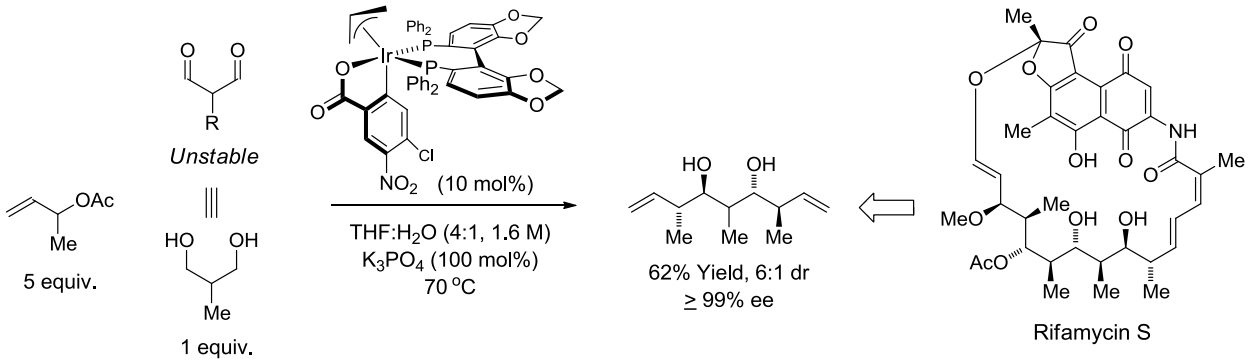
Scheme 1.14 Retrosynthesis of Roxaticin and application of double allylation in synthesis.

The synthesis of bryostatin 7 is accomplished in 20 linear and 36 total steps.[33] The concise nature of this approach can be attributed to the rapid assembly of key fragments **A** and **B**, as availed through application of C-C bond forming hydrogenations. The same double allylation of 1,3-propanediol to form C_2-symmetric diol. Interestingly, ozonolysis of diol **11** delivers an unstable lactol, which is protected *in situ* as the *bis*-TBS ether to provide aldehyde **12** as a single isomer. Transfer hydrogenation in the presence of 1,1-dimethylallene promotes *tert*-prenylation[17b]. Elaboratin of this product by ozonolysis provides *β*-acetoxy aldehyde **14**. Reductive coupling of aldehyde **14** and allyl acetate under transfer hydrogenation conditions results in the formation of homoallylic alcohol **15**, which was elaborated to fragment B of Bryostatin 7 (Scheme 1.15).



Scheme 1.15 Retrosynthesis of bryostatin 7 and application of transfer hydrogenation in synthesis.

Using the chromatographically isolated iridium catalyst modified by (*R*)-SEGPHOS, 1 of 16 possible stereoisomers is formed predominantly.[34] This methodology was used to form the C19-C27 *ansa* chain of rifamycin S in 8 steps (originally prepared in 26 steps), constituting a formal synthesis of the natural product (Scheme 1.16).[35]



Scheme 1.16 Enantioselective double allylation and double crotylation of 1,3-propanediols to form polyacetate and polypropionate building blocks.

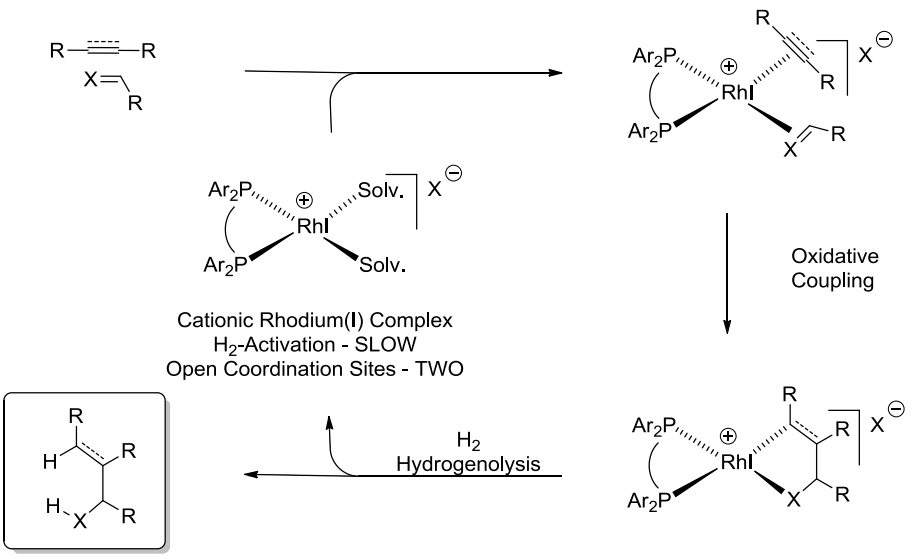
1.6 CONCLUSION

Polyketides are usually biosynthesized through recurring addition of small two to three carbon unit addition through a decarboxylative condensation of malonyl-CoA derived extender units in a similar process to fatty acid synthesis. The polyketide chains produced by a polyketide synthases (PKSs) are often further derivitized and modified into bioactive natural products. Inspired by the process-relevance of hydrogenation and hydroformylation, we have developed a broad, new family of enantioselective C-C bond forming hydrogenation and transfer hydrogenations.The atom-economy associated with these transformations, particularly the exclusion of stoichiometric metallic byproducts, the control of relative and absolute stereocontrol make them a viable candidate in the synthesis of complex molecules, especially in synthesis of polyketide natural products, as shown in the synthesis of roxaticin and bryostatin 7.

Chapter 2: Diastereo- and Enantioselective Rhodium Catalyzed Aldol Coupling Reaction of Enone to Aldehydes *via* Catalytic Hydrogenation

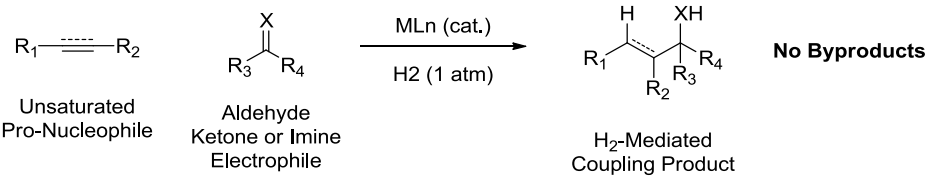
2.1 Introduction

In today's proficient, innovation driven and environmentally conscious chemical society, the focus of chemical research resides to develop a sustainable means of preparing the chemical commodities. Therefore, the focus of many effective researches is to improve upon the present set of principle in chemical transformation to atom economy[36], step economy, green chemical processes and ideal synthesis which avoid the generation of stoichiometric byproducts. An example of such transformation is hydrogenation.[37] In modern chemical transformations catalytic hydrogenation has found broad application across all parts of the chemical industry, especially in the manufacture of chiral pharmaceutical ingredients. In fact, industrial syntheses of more than half of the chiral compounds excluding physical and enzymatic resolution are made via asymmetric hydrogenation.[38] This is the reason why this process is an ideal chemical transformation and avoids the generation of stoichiometric byproducts moreover, hydrogen gas is the cheapest possible reductant. Even though its routine use for well over a century, alkene hydroformylation[39] and the parent Fischer-Tropsch process[40] were the only examples of hydrogen-mediated reductive coupling. The alkene hydroformylation, the prototypical C-C bond forming hydrogenation is the largest volume application of homogenous catalysis.[41] Hence, it became necessary to identify a mechanistic pathway that would unlock hydrogenation for C-C bond formation. Whereas neutral rhodium complexes engage in rapid hydrogen oxidative addition,[42] hydrogen oxidative addition is turnover limiting for cationic rhodium catalysts.[43,44] Consequently, for cationic complexes of rhodium, it was found that the diminished rate of hydrogen oxidative addition, along with the availability of an additional coordination site, promote oxidative coupling to form metallacyclic intermediates, which participate in hydrogenolysis to form products of reductive C-C bond formation in the absence of byproducts (Scheme 2.1).



Scheme 2.1 Cationic rhodium complexes promote hydrogen-mediated reductive coupling via oxidative coupling pathways.

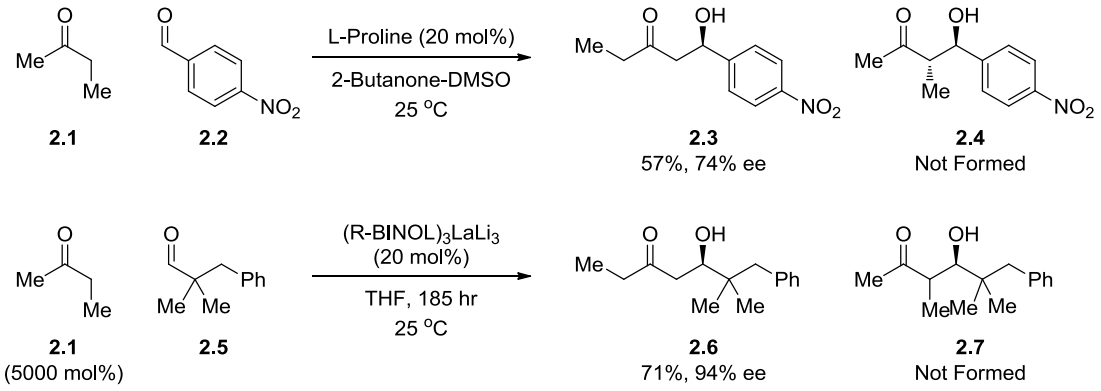
Inspired by the impact of hydrogenation and hydroformylation on industrial chemistry,[45] our research group carried out systematic investigations into reductive C-C bond formation *via* catalytic hydrogenation.[46] Through the implementation of oxidative coupling pathways, our research group has established numerous C-C bond forming hydrogenations. We have found that diverse π-unsaturated reactants can couple to polarized C=X (X = O, NR) bonds under hydrogenation conditions, offering an alternative to stoichiometric organometallic reagents in a broad range of carbonyl and imine addition processes (Scheme 2.2).



Scheme 2.2 Hydrogen mediated C-C bond formation of basic chemical feedstock.

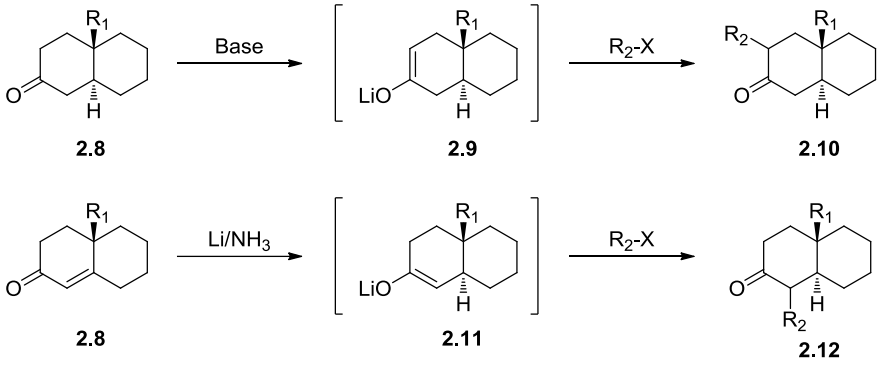
2.2 Background

Aldol reaction[47] is among the versatile chemical transformation available to synthetic community particularly for the synthesis of polyketide natural products. In recent past many advances were made in aldol reaction due to our mechanistic understanding of chemical transformation. This meticulous cross aldol reaction resulted due to development of well-defined enolization protocols, regioselective coupling of enolates, relative and absolute stereocontrol by highly effective chiral auxiliary and ideally metal or organo- catalyzed direct aldol transformation. However, with the evolution of these modern techniques still the aldol reaction lacks a general ideal reactivity. For instance, the site specific enolization in direct aldol addition of non-symmetric ketones remains a significant challenge. Regioselective enolate formation in direct enantioselective aldol additions of nonsymmetric ketones generally favors the sterically less demanding position. For instance, L-proline or the heterobimetallic catalyst $LaLi_3$-tris(binaphthoxide) (LLB) catalyze couling of 2-butanone couple and aldehyde to furnish the linear product[48] (Scheme 2.3).



Scheme 2.3 Linear regiocontrol in direct aldol addition of nonsymmetric ketone

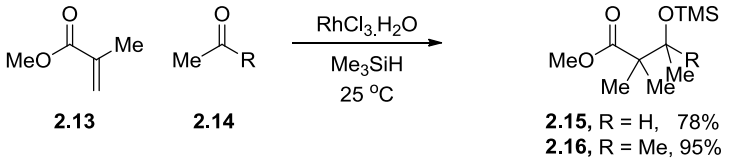
Gilbert Stork reported a solution to this problem by regiospecific enolate formation from an enone.[49] The dissolving metal reduction using Li/NH_3 was found to promote the regiospecific enolate formation, which is impossible to obtain by other methods (Scheme 2.4).



Scheme 2.4 Regiospecific enolate generation using dissolving metal reduction.

2.3 Catalytic Hydrogenative Aldol Coupling Reaction

In 1987, Revis,[15a] benefiting from Stork work, first reported the metal catalyzed reductive coupling of *α,β*-unsaturated esters to carbonyl compounds to form aldol products, termed as the "reductive aldol reaction".[50] In this transformation, $RhCl_3 \bullet 3H_2O$ serves as the precatalyst and trimethylsilane serves as terminal reductant. At ambient temperature, *α,β*-unsaturated esters and lactones were found to couple to both aldehydes and ketones. Notably, as demonstrated by the coupling of methyl methacrylate to acetone, two contiguous tetra-substituted centers may be created in this transformation (Scheme 2.5).



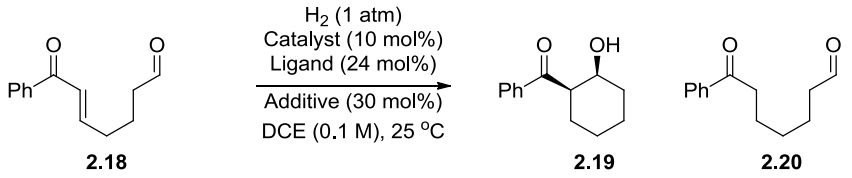
Scheme 2.5 Seminal reductive aldol reaction of methyl acrylate.

2.3.1 Intramolecular Catalytic Hydrogenative Aldol Coupling Reaction of Enones

In order to evaluate the viability, our group investigated the intramolecular enone to aldehyde reductive aldol addition under hydrogenation conditions. Interestingly, employing **2.18** with a neutral complex, Wilkinson catalyst, the reaction mostly delivers the product of conventional hydrogenation **2.20**. However, rhodium salts that embodied increased cationic character, such as $Rh(cod)_2OTf$ provided nearly equal proportions of *syn*-aldol **2.19** and

conventional reduction products **2.20**. Furthermore, when $Rh(cod)_2OTf$ is used in conjunction with basic additive, potassium acetate, the aldol addition product was formed as major reaction product. Using electron deficient ligand, 4-trifluorophenylphosphine the competing reduction pathway was completely suppressed. We found out these reaction condition were applicable to other similar systems[51] (Table 2.1).

Table 2.1 First example of intramolecular catalytic reductive aldol keto-aldehyde cyclization.

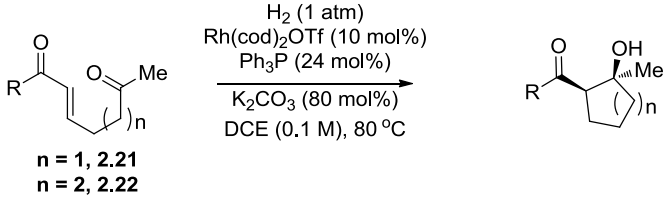


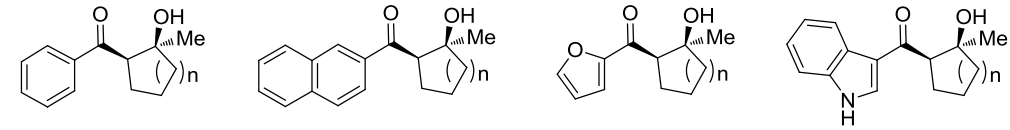
2.18 **2.19** **2.20**

Catalyst	Ligand	Additve	Yield of Aldol (syn-anti)	Yield of 1,4-reduction
$Rh(PPh_3)OTf$	--	--	1% (99:1)	57%
$Rh(PPh_3)OTf$	PPh_3	--	21% (99:1)	25%
$Rh(PPh_3)OTf$	PPh_3	KOAc	59% (58:1)	21%
$Rh(PPh_3)OTf$	$(p\text{-}CF_3\text{-}Ph)_3P$	--	57% (14:1)	21%
$Rh(PPh_3)OTf$	**$(p\text{-}CF_3\text{-}Ph)_3P$**	**KOAc**	**89% (10:1)**	**0.1%**

Additionally, our group has found reductive aldol cyclization of keto-enones, under slightly modified conditions. Using keto-enone **2.21** under slightly different condition, we obtained the *syn*-aldol product **2.22** as single diastereomers, with small quantities of conjugate reduction product (8%) (Table 2.2). The competitive 1,4-redution products resulted since the ketone are less electrophilic as compared to aldehydes.[52]

Table 2.2 Reductive aldol cyclizatio of keto-enones *via* catalytic hydrogenation, yield of conjugate reduction product is indicated in parentheses.





2.22, n = 1, 75% (8%)
2.23, n = 2, 72% (20%)

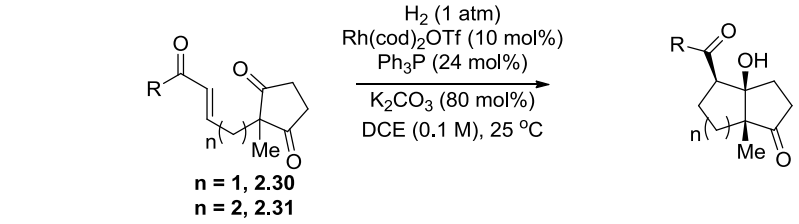
2.24, n = 1, 74% (18%)
2.25, n = 2, 78% (18%)

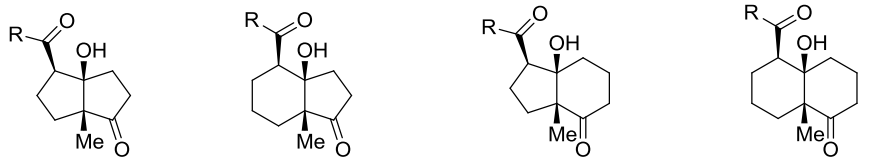
2.26, n = 1, 70% (24%)
2.27, n = 2, 83% (8%)

2.28, n = 1, 74% (8%)
2.29, n = 2, 72% (17%)

However, 1,3-diones **2.30** and **2.31** are more electrophilic due to inductive effect and dipole-dipole interactions, they can reductively cyclized under very similar condition in addition to at ambient temperature provided mainly the desired reductive product with minimal to no conjugate reduction product **2.32** (R = Ph). However, in generation of decaline system **2.37** which are more seterically demanding we observed some extent of conjugate reduction (Table 2.3).[17] Our research group was able to perform similar intramolecular coupling reaction,[53] among them the much challenging addition of aldehyde enolate to ketones to deliver the corresponding reductive aldol cyclization product along with variable amount of conjugate reduction product.

Table 2.3 Reductive aldol cyclization of dione-enones *via* catalytic hydrogenation.





2.32, R = Ph, 84%
2.33, R = Me, 88%

2.34, 86%

2.35, R = Ph, 81%
2.36, R = Me, 73%

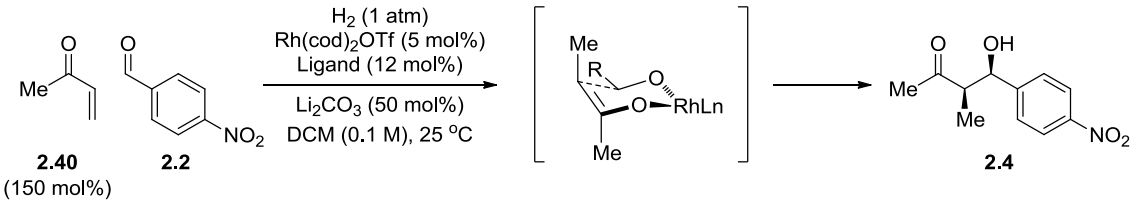
2.37, 65% (15%)

The conventional reduction product is shown in parentheses

2.3.2 Intermolecular Catalytic Hydrogenative Aldol Reaction of Enones

Based on the intermolecular hydrogenative aldol reaction, our group have developed more desirable intermolecular variant which is much needed tool for the construction of polypropionate natural products. For the reaction of methyl vinyl ketone **2.40** and aldehyde **2.2** the previously employed catalyst $Rh(cod)_2OTf$ and triphenylphosphine provided good yield of aldol product **2.4** as mixture of diastereomers. However, with ligand screening it was found that π-acidic ligands such as tri(2-furyl)phosphine promote exceptionally high level of *syn* diasteroselectivity. It was reasoned that the π-acidic ligand may increase the diastereoselectivity by increasing the Lewis acidity at the rhodium center, which should result in compact chair like transition state resulting in destabilization of the competitive pathways. Based on these finding the our group was able to couple methyl vinyl ketone **2.40** (MVK) and ethyl vinyl ketone **2.40a** (EVK) to a wide variety of aldehydes (Table 2.4).[18c] In subsequent work, the scope of high diastereoslective reaction was extended to coupling of MVK and EVK to α-chiral amino aldehydes[18d] and coupling of crotyl vinyl ketone[18e] to wide variety of aldehydes.

Table 2.4 Intermolecular *syn*-diastereoselective reductive aldol reaction. Tri(2-furyl)phosphine effect on diastereoselectivity.



Ligand	Yield (%)	**2.4**, dr
Ph_3P	31	3:1
(2-Fur)Ph_2P	24	6:1
(2-Fur)$_2$PhP	52	15:1
(2-Fur)$_3$P	**74**	**19:1**

2.4 Diastereo- and Enantioselective Rhodium Catalyzed Aldol Reaction of Enone

Enantioselective reductive aldol couplings of vinyl would enable access to branched aldol adducts, providing regiochemical complement to direct organocatalyzed and metal catalyzed aldol couplings of nonsymmetric ketones. However, due to our understanding of hydrogenative aldol reaction the enantioselective variant is specially challenging. The problem poses the following problems,

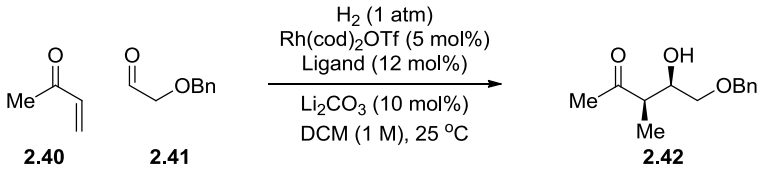
a) Chelating phosphine ligands provides only trace quantities of product.
b) Diastereoselectivity can be enforced by using π-acidic ligands, such as tri(2-furyl)phosphine.
c) Monodentate chiral phosphine ligands having π-acidic character are commercially limited.

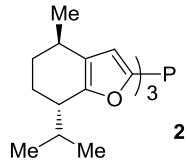
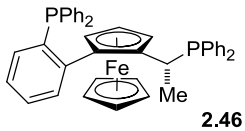
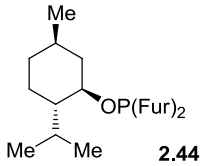
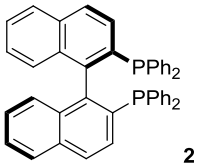
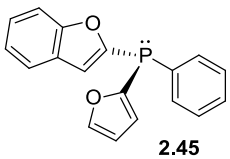
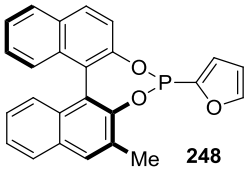
Therefore, the task of design, synthesis and evaluation of novel chiral monodentate phosphine ligand were considered.

2.4.1 Identification of Lead Chiral Monodentate Phosphine Ligand

The enantioselective hydrogenative aldol reaction evaluation starts with screening with different π-acidic chiral ligand. Methyl vinyl ketone **2.40** and 2-benzyloxyacetaldehyde **2.41** was couple under previously optimized hydrogenation condition varying the chiral ligand. Some of these ligands were effective, displaying low to moderate selectivity. As proposed, bidentate ligands **2.46** and **2.47** were not effective resulting in low conversion (Table 2.5, entries 4 and 5). However, monodentate ligands resulted in good yields though, the enantioselectivity was low. The best ligand in terms of enantiocontrol was furyl substituted BINAP based phosphonite structure **2.48** (Table 2.5, entry 6). However, over the years numerous ligands were modified and screened without any promising improvement.

Table 2.5 Initial screening of ligands for enantioselective aldol reaction.

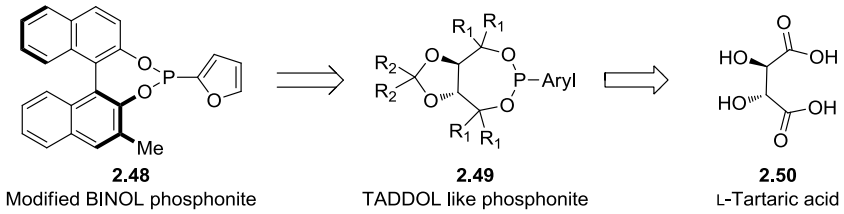


Entry	Ligand	Yield	Entry	Ligand	Yield
1	 **2.43**	64%, 4:1dr 30%ee	4[a]	 **2.46**	trace
2[a]	 **2.44**	80%, 8:1dr 42%ee	5[a]	 **2.47**	10%, 3:1dr 27%ee
3[a]	 **2.45**	85%, 18:1dr 6%ee	6[a]	 **248**	79%, 8:1dr 43%ee

[a]Reaction were conducted by Dr. Cisco Bee and Dr. Hiroki Lida

Further considering the best ligand **2.48** in table 2.5 (entry 6) left us considering if it can be refined into a system that can easily modified with different structural variation, which will enable us to investigate well defined structure selectivity relationships. A comparable structure

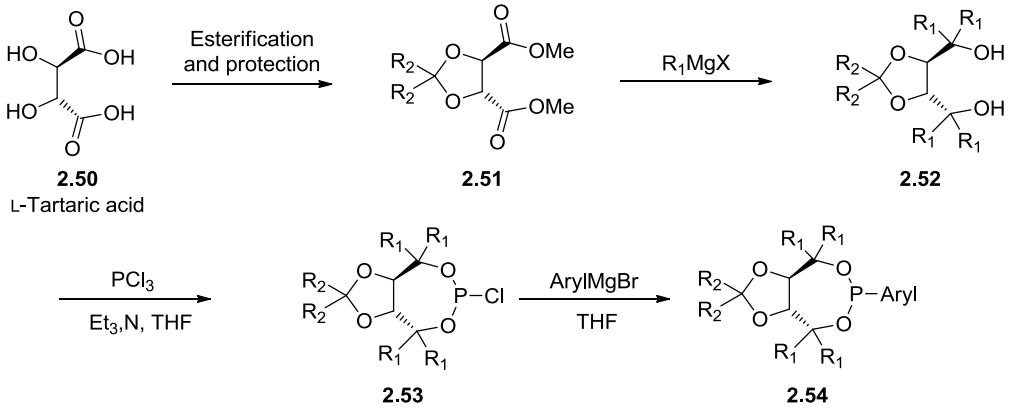
unit is TADDOL like phosphonites[54] **2.49,** offer a versatile template amenable to systematic structural variation that may be independently optimized; a) the P-aryl unit (Aryl), b) the groups appended to the tertiary carbinol center (R_1) and c) the ketal substructure (R_2), scheme 2.6. Additionally, it might be possible to combine the independently optimized units to in a ligand augmenting the effect of individual subunits.



Scheme 2.6 TADDOL like phosphonite ligand.

2.4.2 Ligand Optimization: Structure Selectivity Relationship

The chiral phosphonite ligands were synthesized from chiral pool, starting from L-Tartaric acid **2.50**. The synthesis involved conventional transformations to the desire ligands **2.54**. It is important to note that the synthesis is very divergent and the different structural unit can be installed with slight modification. The synthesis outline is given in scheme 2.7.

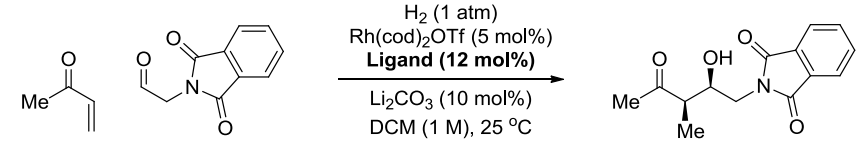


Scheme 2.7 General synthesis scheme for TADDOL like phosphonite ligand.

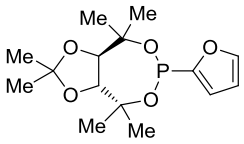
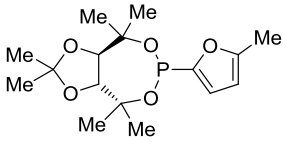
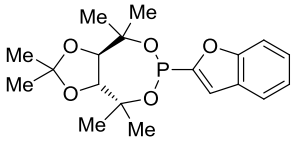
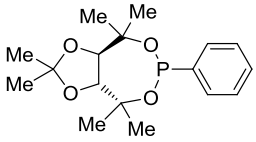
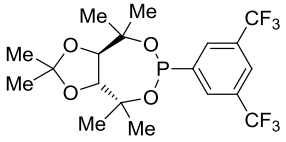
The structural modification started with *P*-aryl moiety while R_1 and R_2 were fixed as methyl groups. We know beforehand that 2-furyl is vital for reactivity and enantioselectivity. Therefore, the very first ligand, 2-furyl substituted phosphonite ligand **2.57** was synthesized and

to our delight it gave excellent reactivity with moderate selectivity (90%, 59% ee) (Table 2.6, entry 1). Encouraged by this finding we prepared and screened different *P*-aryl substituted ligands. 2-methyl furyl gave poor selectivity **2.58** (50% ee) (Table 2.6, entry 2), while changing the furyl group to benzofuryl **2.59**, resulted in good selectivity (66% ee) (Table 2.6, entry 3). The phenyl group **2.60** at this position gave very high selectivity (80% ee) however poor reactivity (20% yield) (Table 2.6, entry 4). Also, electron withdrawing substituted phenyl group **2.61** were also ineffective (Table 2.6, entry 5).

Table 2.6 Effect of *P*-aryl subunit on structure selectivity relationship in TADDOL like phosphonite ligands.



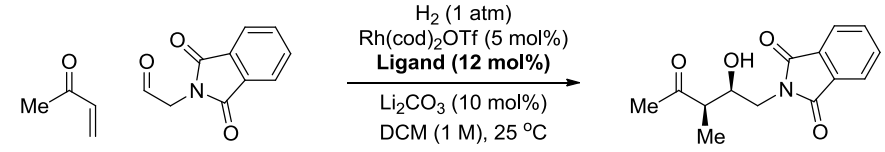
2.40 (150 mol%) **2.55** **2.56**

Entry[a]	Ligand		Yield (%)	%ee
1		**2.57**	90	59
2		**2.58**	52	50
3		**2.59**	**64**	**66**
4		**2.60**	20	80
5		**2.61**	30	45

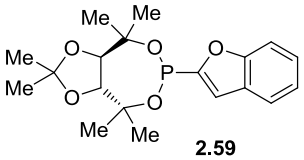
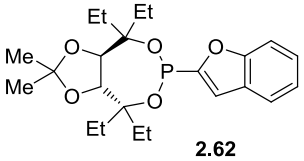
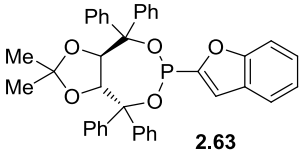
[a]Reaction were conducted by Dr. Cisco Bee and Dr. Soo Bong

The benzofuryl substituted ligand **2.57** was not only superior at chirality transfer but from experimental point of view, this ligand was also more stable than for example the 2-furyl substituted ligand. Having established the benzofuryl group next the R_1 and R_2 groups were investigated. By changing R_1 group from methyl to ethyl **2.62** which in turn increase the steric bulk at the phosphine center resulted in poor reactivity with 32%, though with slight increase in selectivity (76% ee, table 2.7, and entry 2). However, with introduction of even bulkier subunit like phenyl group **2.63** both the selectivity and reactivity decreases (15%, 30% ee, table 2.7, entry 3). Therefore, the methyl subunit was considered to be optimal at R_1 position.

Table 2.7 Effect of R_1 subunit on structure selectivity relationship in TADDOL like phosphonite ligands.



2.40 (150 mol%) **2.55** **2.56**

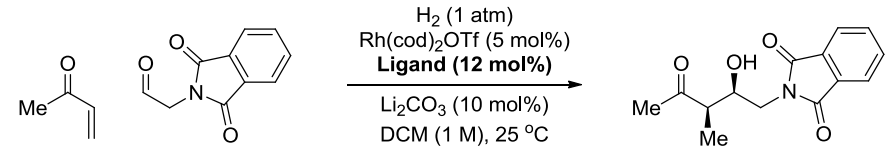
Entry	Ligand	Yield (%)	%ee
1[a]	 **2.59**	**64**	**66**
2	 **2.62**	32	76
3[a]	 **2.63**	15	30

[a]Reaction were conducted by Dr. Cisco Bee and Dr. Soo Bong

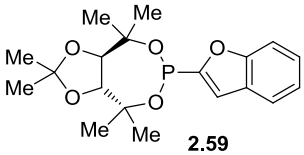
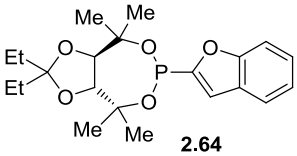
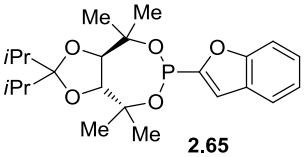
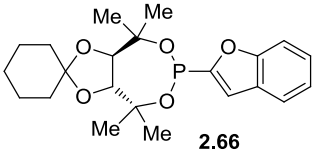
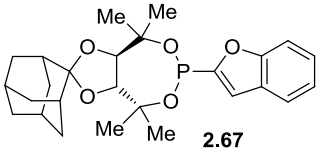
Finally, the ketal substructure (R_2) groups were established. When the size of the group was increased from methyl to ethyl **2.64**, the selectivity and reactivity (75% ee, 75% yield) saw a considerable jump (Table 2.8, entry 2). However, further increasing the size to *i*-propyl group in

ligand **2.65** did not help to increase neither the reactivity nor selectivity (Table 2.8, entry 3). It was also found that cyclic ketals such as cyclohexyl group **2.66** resulted in moderate selectivity (56% ee, table 2.8, entry 4). The very sterically demanding adamantyl group **2.67** also displayed only moderate reactivity and selectivity (Table 2.8, entry 5). Based on these findings, ethyl group was established as the optimal R_2 group.

Table 2.8 Effect of R_2 subunit on structure selectivity relationship in TADDOL like phosphonite ligands.



2.40 (150 mol%) **2.55** **2.56**

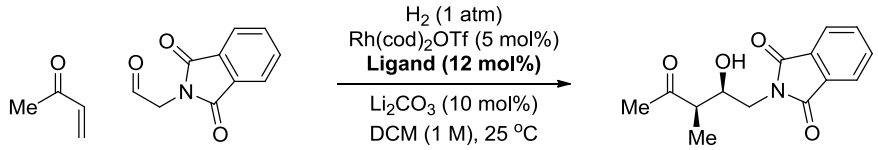
Entry	Ligand	Yield (%)	%ee
1[a]	 **2.59**	64	66
2	 **2.64**	**75**	**75**
3[a]	 **2.65**	76	30
4	 **2.66**	90	56
5[a]	 **2.67**	73	57

[a]Reaction were conducted by Dr. Cisco Bee and Dr. Soo Bong

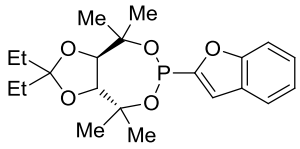
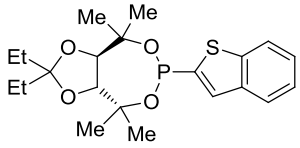
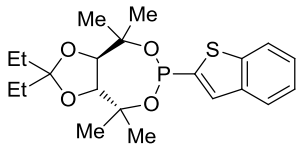
Interestingly, the ligand which combines the optimal 2- benzofuryl, diethyl ketal, and dimethyl carbinol substructures **2.64**, gave the best results, still the selectivity was not practical.

Further screening of the aryl group revealed that the benzothiophene *P*-aryl substituent ligand gave better selectivity than benzofuran (Table 2.9, entry 2). This ligand was named as **Abbasphos I (AP-I).** Finally at this point, we anticipated optimization of reaction condition will result in higher selectivity. Satisfyingly, at 0 ^{o}C we were able to obtained very high selectivity (94%, 94% ee) (Table 2.9, entry 3). Further, the optimal efficiency and selectivity were observed using the preformed **Rh complex** derived from $Rh(cod)_2OTf$ and benzothiophene substituted ligand **AP-I** as a precatalyst. Under these reaction conditions, the parent aldehyde is transformed to the *syn*-aldol adduct with exceptional levels of relative and absolute stereocontrol (Table 2.9, entry 4).

Table 2.9 The 2-benzotheinyl group and reaction condition optimization.



2.40 (150 mol%) **2.55** **2.56**

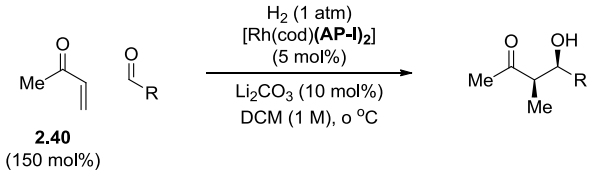
Entry	Ligand		T (^{o}C)	Yield (%)	%ee
1		**2.64**	25	75	75
2		**(AP-I)**	25	90	86
3[a]		**(AP-I)**	0	94	94
4[a]	[Rh(cod)**(AP-I)$_2$**]	**2.68**	0	88	96

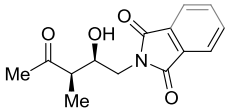
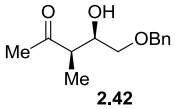
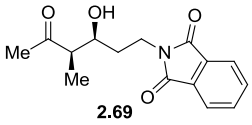
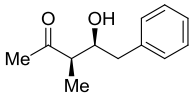
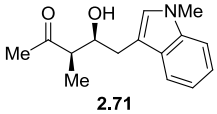
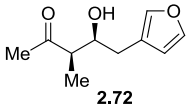
[a]Reaction were conducted by Dr. Soo Bong

2.4.3 Substrate Scope

The optimal chiral TADDOL like phosphonite (**AP-I**) ligated Rh complex was examined in reductive aldol couplings of MVK to diverse aldehydes. The reaction resulted in uniformly high relative and absolute selectivities across a wide range of aldehydes. Beyond the parent aldehyde **2.56** and 2-benzyloxy acetaldehyde **2.42** (Table 2.10, entry 1 and 2), β-heteroatom substituted aldehyde **2.69** (Table 2.10, entry 3) and α-(hetero)aryl aldehydes **2.70**-**2.72** (Table 2.10, entry 4, 5 and 6) all were found to engage in highly diastereo- and enantioselective hydrogenative aldol additions.

Table 2.10 Diastereo and Enantioselective aldol coupling of MVK to aldehydes.

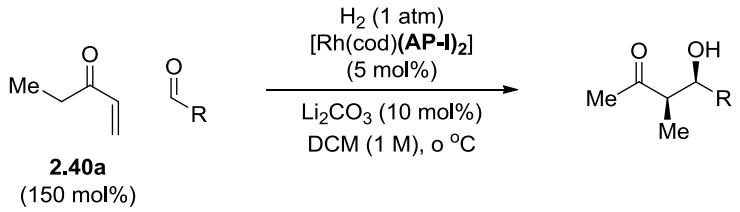


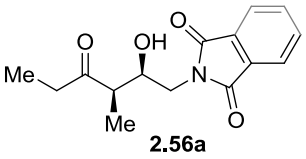
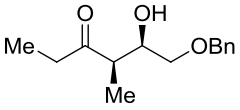
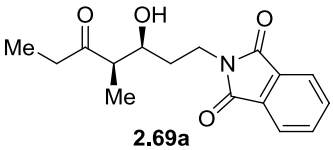
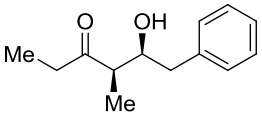
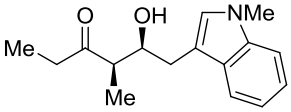
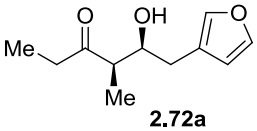
Entry	Ligand	Yield (%)	dr	%ee
1	 **2.56**	88	50:1	96
2[a]	 **2.42**	85	25:1	91
3	 **2.69**	88	50:1	85
4[a]	 **2.70**	70	25:1	90
5	 **2.71**	92	15:1	87
6[a]	 **2.72**	79	11:1	87

[a]Reaction were conducted by Dr. Cisco Bee and Dr. Soo Bong

A similar set of reactions were performed with ethyl vinyl ketone **2.40a** under the optimized reaction conditions. Uniform levels of relative and absolute stereocontrol were observed in the hydrogenative aldol additions (Table 2.11).

Table 2.11 Diastereo and Enantioselective aldol coupling of EVK to aldehydes.



Entry	Ligand	Yield (%)	dr	%ee
1	 **2.56a**	94	45:1	94
2[a]	 **2.42a**	96	21:1	88
3	 **2.69a**	96	25:1	92
4[a]	 **2.70a**	76	22:1	90
5	 **2.71a**	97	25:1	90
6[a]	 **2.72a**	83	25:1	88

[a]Reaction were conducted by Dr. Cisco Bee and Dr. Soo Bong

2.4.4 Second generation of TADDOL like Phosphonite Ligands

The Single crystal X-ray diffraction analysis of [Rh(cod)$(L)_2$]OTf (L = the acetonide of **AP-I**) reveals a C_2-symmetric arrangement around Rh (Figure 2.1). Based upon the hypothesis that a similar metal-ligand arrangement is evident in the stereo-determining event, ligands **AP-II** and **AP-IV** were also designed. For ligands **AP-II** and **AP-IV** the (benzo)thiophene moiety is substituted such that the purported chiral pocket is deepened, thus potentially conferring heightened levels of enantioselection.

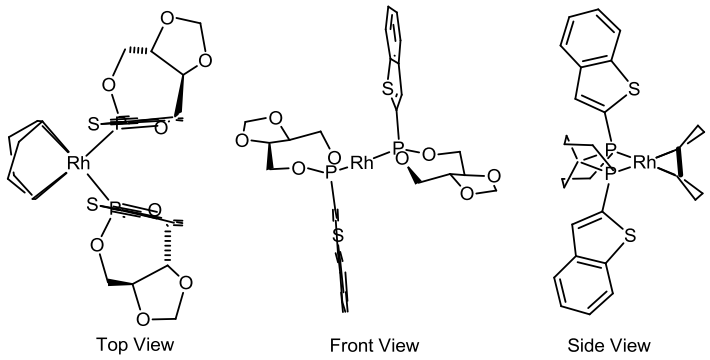
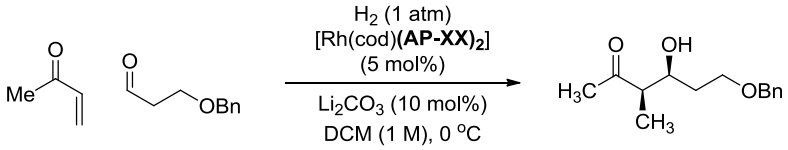


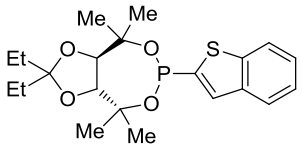
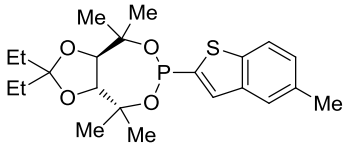
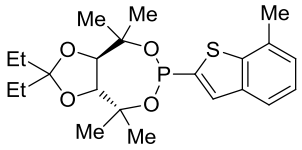
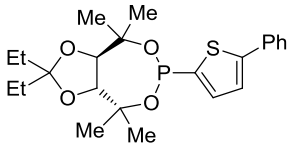
Figure 2.1 Structure of [Rh(cod)$(L)_2$]OTf (L = the acetonide of **AP-I**) determined by X-ray diffraction reveals C_2-symmetric arrangement.[a] ([a]The figure graphics are depictions of crystallographic data imported into ChemDraw Ultra 9.0. For clarity, the following substructures were omitted. Top: The methyl groups and triflate ion. Front: The methyl groups, triflate ion and COD. Side: The methyl groups, triflate ion, dioxolane rings and phosphonite oxygen atoms.)

The reliability of this analysis is supported by the fact that **AP-II** and **AP-IV** are both found to induce higher levels of optical enrichment in aldehyde **2.73**, whereas **AP-III**, which projects the methyl residue into an inactive volume of space, displays selectivities comparable to those of **AP-I** (Table 2.12).

Table 2.12 Second generation of TADDOL like phosphonite ligands with improve selectivity.



2.40 (150 mol%) **2.73** **2.74**

Entry	Ligand		Yield (%)	dr	%ee
1		**(AP-I)**	63	10:1	57
2[a]		**(AP-III)**	43	8:1	66
3[a]		**(AP-II)**	51	15:1	80
4		**(AP-IV)**	89	22:1	88

[a]Reaction were conducted by Dr. Cisco Bee and Dr. Soo Bong

2.5 Summary

In summary, we report the first distereo- and enantioselective reductive aldol couplings of commercially available methyl vinyl ketones (MVK) and ethyl vinyl ketone (EVK), This was achieved through the design of a novel monodentate TADDOL-like phosphonite ligand. In the presence of aldehydes and vinyl ketone using cationic rhodium catalysts modified by chiral TADDOL-like phosphonite ligands produces aldol adducts with excellent control of relative and absolute stereochemistry. In the course of designing the novel monodentade TADDOL-like phosphonite ligand (abbasphos) a structure reactivity relationship of the ligand with respect to absolute stereocontrol was displayed. These ligands enabled us to couple aliphatic, aromatic and

heteroaromaatic aldehyde in very high enantiocontrol and high yields. Further, developments of second generation Abbasphos ligands were exhibited with higher selectivity.

2.6 Experimental Scetion

2.6.1 General Procedure for Asymmetric Aldol Coupling of Enones and Aldehydes

To a 13 mm × 100 mm test-tube were added Li_2CO_3 (10 mol%), [Rh(cod)(AP-I)$_2$]OTf (5 mol%), aldehyde (100 mol%) and DCM (1.0 M). The test-tube was sealed, cooled to 0 ^oC and the reaction system was sparged with Ar(g) followed by H_2(g) for 20 seconds each. The reaction system was placed under one atmosphere of hydrogen using a balloon and enone (300 mol%) was added to the reaction mixture. The reaction mixture was allowed to stir for 24 h at 0 ^oC. The reaction mixture was evaporated and the aldol products were separated by flash chromatography (SiO_2: EtOAc/Hexane).

2.6.2 General Procedure for the determination of Enantiomeric Excess for Compounds

Enantioselectivities were determined by chiral stationary phase HPLC analyses made in comparison to racemic diastereomeric mixtures prepared by (i) hydrogenation of the corresponding Morita-Baylis-Hillman adducts, or in the case of the ethyl vinyl ketone adducts **1c**-**7c** (ii) the aldol reaction between the lithium enolate of 3-pentanone and the corresponding aldehyde, followed by treatment with magnesium bromide etherate. The enantiomeric excess reported for all products is based on the average of two reactions, with a minimum of two HPLC analyses per reaction (averaged). In all cases the enantiomeric excess did not vary more than 2% between runs.

2.6.3 Experimental Procedures for Catalyst Formation

General Procedure for the Formation of [Rh(cod)(AP-I)$_2$]OTf complex

(3a*R*,8a*R*)-6-(Benzo[b]thiophen-2-yl)-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (AP-I) (700 mg, 1.7 mmol, 210 mol%) and Rh(cod)$_2$OTf (375 mg, 0.8 mmol, 100 mol%) were dissolved in DCM (0.1 M) and stirred for 6 h at 25 ^{o}C. The solvent was removed under reduced pressure and the residue was triturated with dry degassed hexanes for 10 h with vigorous stirring. The resulting mixture was filtered, and the solid was dried under vacuum to give the product as a yellow powder (775 mg, 82% yield).

[Rh(cod)(AP-I)$_2$]OTf

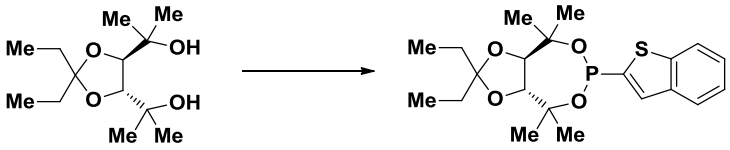
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.9 Hz, 2H), 7.65 (d, *J* = 7.9 Hz, 2H), 7.46-7.36 (m, 6H), 5.55 (bs, 2H), 5.47 (bs, 2H), 3.86 (d, *J* = 9.2 Hz, 2H), 3.74 (d, *J* = 9.2 Hz, 2H), 2.70-2.50 (m, 8H), 1.51 (m, 14H), 1.25 (m, 12H), 1.06 (s, 6H), 0.79 (q, *J* = 8.2 Hz, 12H). **^{31}P NMR** (121.5 MHz, $CDCl_3$): δ 116.2 (d, $J_{P\text{-}Rh}$ = 220.0 Hz). **MP**: 142-146 ^{o}C (dec).

[Rh(cod)(AP-IV)$_2$]OTf

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.59 (m, 4H), 7.44-7.36 (m, 10H), 5.55 (bs, 2H), 5.42 (bs, 2H), 3.89 (d, *J* = 9.4Hz, 2H), 3.78 (d, *J* = 9.4Hz, 2H), 2.69-2.52 (m, 8H), 1.62 (m, 8H), 1.52 (s, 6H), 1.39 (s, 6H), 1.31 (s, 6H), 1.14 (s, 6H), 0.85 (t, *J* = 7.4Hz, 6H), 0.84 (t, *J* = 7.0 Hz, 6H). **^{31}P NMR** (121.5 MHz, $CDCl_3$): δ 123.1 (d, $J_{P\text{-}Rh}$ = 219.7 Hz). **MP**: 137-139 ^{o}C.

2.6.4 Spectroscopic Data and Experimental Procedures for Selected Chiral Ligands

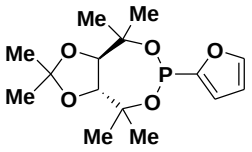
a) Representative procedure for the synthesis of Chiral Ligands:



To a solution of (4*R*,5*R*)-diethyl- 2,2-dimethyl-1,3-dioxolane-4,5-dipropan-2-ol (4.0 g, 16.2 mmol, 100 mol%) and triethylamine (6.8 mL, 48.6 mmol, 300 mol%) in THF (0.1 M) at -78 ^{o}C, PCl_3 (2.2 mL, 20.0 mmol, 120 mol%) was added quickly with stirring, and the reaction was allowed to come to 25 ^{o}C over 1 hour, and then was stirred for 10 hours at 25 ^{o}C. The reaction was then filtered through a plug of celite under an argon atmosphere with the exclusion of moisture, and the solvent was removed via distillation at reduced pressure. The crude solid was then dissolved in 50 mL of ether, and the solids were removed by filtration through a plug of celite under an argon atmosphere with the exclusion of moisture. The solvent was again removed under reduced pressure. The resulting oil (3a*R*,8a*R*)-6-chloro-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine (4.9 g, 15.8 mmol) was of sufficient purity to be used directly in the next step.

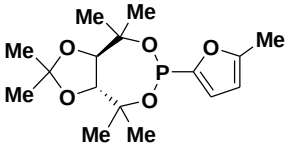
To benzothiophene (1.65 g, 12.3 mmol, 100 mol%) dissolved in THF (0.1 M) and cooled to -78 ^{o}C, *tert*-butyllithium (1.2 M, 10.2 mL, 12.2 mmol, 100 mol%) was added dropwise and the mixture was stirred for 1 hour at -78 ^{o}C. This solution was then transferred via cannula quickly to a solution of (3a*R*,8a*R*)-6-chloro-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine (4.9 g, ~15.8 mmol, 100 mol%) in THF (0.1 M) at -78 ^{o}C. The reaction was allowed to warm to 25 ^{o}C over 1 hour, and then stirred for 10 hours at 25 ^{o}C. The solvent was then removed under reduced pressure and the crude product was purified by flash chromatography (SiO_2: Ether/Hexane) to give the title compound in 59% yield over 2 steps (3.88 g, 9.5 mmol).

(3a*R*,8a*R*)-6-(furan-2-yl)-tetrahydro-2,2,4,4,8,8-hexamethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.57



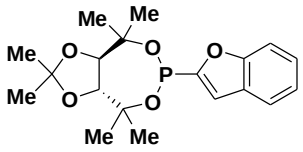
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 1.4 Hz, 1H), 6.84-6.81 (m, 1H), 6.42–6.40 (m, 1H), 4.46 (dd, *J* = 9.2, 3.7 Hz, 1H), 3.99 (d, *J* = 9.2 Hz, 1H), 1.53 (s, 6H), 1.44 (s, 3H), 1.41 (s, 6H), 1.35 (S, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.6 (d, *J* = 11.2 Hz), 146.7 (d, *J* = 4.5 Hz), 118.2 (d, *J* = 26.9 Hz), 110.1 (d, *J* = 5.2 Hz), 109.7, 82.5 (d, *J* = 3.7 HZ), 81.8 (d, *J* = 22.4 Hz), 76.5 (d, *J* = 4.5 Hz), 76.4 (d, *J* = 6.7 Hz), 29.9 (d, *J* = 3.0 Hz), 29.0 (d, *J* = 3.0 Hz), 27.3, 27.1, 23.2, 19.8 (d, *J* = 9.7 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$): δ 134.6. **HRMS** calcd for $C_{15}H_{24}O_5P$ (M+1): 315.1361, Found: 315.1366. **FTIR** (neat): 2980, 2936, 2884, 1456, 1370, 1243, 1560, 1071, 1041, 1010, 972, 926, 906, 883, 829, 750, 743 cm^{-1}. **MP:** 55-58 ^{o}C. **$[\alpha]_D^{25}$** +12^{o}, c = 0.83 in DCM

(3a*R*,8a*R*)-tetrahydro-2,2,4,4,8,8-hexamethyl-6-(5-methylfuran-2-yl)-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine], 2.56



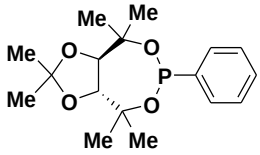
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71-6.75 (m, 1H), 6.01-6.00 (m, 1H), 4.45 (d, *J* = 9.2, 3.7 Hz, 1H), 3.98 (d, *J* = 9.2 Hz, 1H), 2.35 (s, 3H), 1.55 (s, 3H), 1.53 (s, 3H), 1.45 (s, 3H), 1.41 (s, 6H), 1.35 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.2 (d, *J* = 4.5 Hz), 153.7 (d, *J* = 10.5 Hz), 120.1 (d, *J* = 29.9 Hz), 109.6, 106.6 (6.7 HZ), 82.4 (d, *J* = 4.5 Hz), 81.8 (d, *J* = 22.4), 76.4 (d, *J* = 4.5 Hz), 76.2 (d, *J* = 6.0 Hz), 29.9 (d, *J* = 3.0 Hz), 29.0 (d, *J* = 3.0 Hz), 27.3, 27.1, 23.2, 19.8 (d, *J* = 10.5 Hz), 13.9. **^{31}P NMR** (121.5 MHz, $CDCl_3$): δ 132.1. **HRMS** calcd for $C_{16}H_{26}O_5P$ (M+1): 329.1518, Found: 329.1520. **FTIR** (neat): 2986, 2935, 1508, 1374, 1242, 1169, 1145, 1078, 1015, 935, 878, 627 cm^{-1}.**MP**: 57-59 ^{o}C. **$[\alpha]_D^{25}$** +5.0^{o}, c = 1.0 in DCM

(3a*R*,8a*R*)-6-(benzofuran-2-yl)-tetrahydro-2,2,4,4,8,8-hexamethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.59



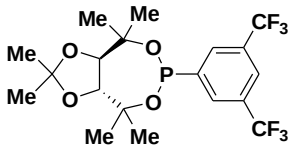
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (dm, *J* = 7.8, 1H), 7.55 (dm, *J* = 8.2 Hz, 1H), 7.32 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H), 7.24-7.18 (m, 2H), 4.49 (dd, *J* = 9.4, 3.7 Hz, 1H), 4.02 (d, *J* = 9.2 Hz, 1H), 1.58 (s, 6H), 1.48 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.2 (d, *J* = 13.5 Hz), 157.3 (d, *J* = 3.7 Hz), 127.2 (d, *J* = 6.0 Hz), 125.6, 122.9, 121.8, 114.2 (d, *J* = 23.9 Hz), 112.0, 109.9, 82.5 (d, *J* = 4.5 Hz), 82.0 (*J* = 22.4 Hz), 30.0 (*J* = 3.0 Hz), 29.1 (d, *J* = 3.0 Hz), 27.4, 27.2, 23.2 (2C), 19.9, 19.8. **^{31}P NMR** (121.5 MHz, $CDCl_3$): δ 136.8. **HRMS** calcd for $C_{19}H_{26}O_5P$ (M+1): 365.1518, Found: 365.1519. **FTIR** (neat): 2984, 2974, 1540, 1374, 1236, 1171, 1089, 979, 794, 753, 641 cm^{-1}. **MP**: 72–75 ^{o}C. **$[\alpha]_D^{25}$** +12^{o}, c = 0.50 in DCM

(3a*R*,8a*R*)-tetrahydro-2,2,4,4,8,8-hexamethyl-6-phenyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.60



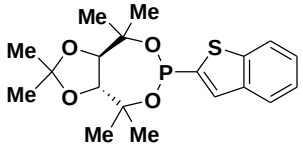
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.60 (m, 2H), 7.40-7.37 (m, 3H), 4.54 (dd, *J* = 9.4, 3.9 Hz, 1H), 3.95 (d, *J* = 9.2 Hz, 1H), 1.56 (s, 6H), 1.45 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 140.9 (d, *J* = 6.0 Hz), 130.4, 129.7 (d, *J* = 23.9 Hz), 128.2 (d, *J* = 7.5 Hz), 109.6, 82.6 (d, *J* = 3.7 Hz), 82.0 (d, *J* = 22.4 Hz), 76.4 (d, *J* = 4.7 Hz), 76.2 (d, *J* = 5.2 Hz), 30.2 (d, *J* = 3.0 Hz), 29.1 (d, *J* = 3.0 Hz), 27.3, 27.2, 23.3 (2C), 20.1, 20.0. **^{1}P NMR** (121.5 MHz, $CDCl_3$): δ 131.6. **HRMS** calcd for $C_{17}H_{26}O_4P$ (M+1): 325.1569, Found: 325.1568. **FTIR** (neat): 2982, 2974, 1520, 11282, 1231, 1171, 1042, 997, 792, 638 cm^{-1}. **MP**: 62–64 ^{o}C. **$[\alpha]_D^{25}$** +18^{o}, c = 0.4 in DCM

(3a*R*,8a*R*)-6-(3,5-bis(trifluoromethyl)phenyl)-tetrahydro-2,2,4,4,8,8-hexamethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.61



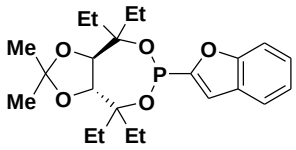
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (m, 2H), 7.89 (s, 1H), 4.52 (dd, *J* = 9.2 Hz, 1H), 3.96 (d, *J* = 9.2 Hz, 1H), 1.59 (s, 6H), 1.48 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 144.4 (d, *J* = 14.2 Hz), 131.4 (qd, *J* = 33.7, 6.0 Hz, 2C), 130.0 (dm, *J* = 23.2 Hz, 2C), 124.0 (m), 123.3 (q, *J* = 273.0 Hz, 2C), 110.0, 82.6, 82.0 (d, *J* = 21.6 Hz), 77.3 (d, *J* = 3.7 Hz), 77.2 (d, *J* = 5.2 Hz), 30.0 (d, *J* = 3.0 Hz), 29.2 (d, *J* = 3.0 Hz), 27.3, 27.1, 23.2, 20.0 (d, *J* = 9.7 Hz). **^{31}P NMR** (161 MHz, $CDCl_3$): δ 147.0. **HRMS** calcd for $C_{19}H_{24}O_4F_6P$ (M+1): 461.1316, Found: 461.1287. **FTIR** (neat): 2988, 2940, 2896, 1456, 1372, 1280, 1136, 1078, 1016, 973, 936, 905, 835, 812, 742, 703, 682, 608 cm^{-1}. **MP**: 101-105^{o}C (dec). **$[\alpha]_D^{25}$** +23^{o}, c = 0.83 in DCM

(3a*R*,8a*R*)-6-(benzo[b]thiophen-2-yl)-tetrahydro-2,2,4,4,8,8-hexamethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, AP-Ia



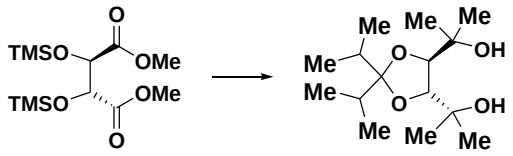
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.83 (m, 1H), 7.81-7.77 (m, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.36-7.30 (m, 2H), 4.49 (dd, *J* = 9.3, 3.5 Hz, 1H), 3.99 (d, *J* = 9.3 Hz, 1H), 1.57 (s, 6H), 1.46 (s, 3H), 1.43 (s, 6H), 1.36 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 144.3 (d, *J* = 26.9 Hz), 142.7, 139.5 (d, *J* = 10.5 Hz), 130.4 (d, *J* = 36.7 Hz), 125.3, 124.4, 124.1, 122.5, 109.8, 82.5 (d, *J* = 4.5 Hz), 82.1, 81.9, 76.8 (d, *J* = 12.7 Hz), 30.1 (d, *J* = 3.0 Hz), 29.2 (d, *J* = 3.0 Hz), 27.4, 27.2, 23.2, 20.0 (d, *J* = 9.7 Hz). **^{31}P NMR** (161 MHz, $CDCl_3$): δ 143.4. **HRMS** calcd for $C_{19}H_{26}O_4PS$ (M+1): 381.1289, Found: 381.1286. **FTIR** (neat): 2982, 2976, 1506, 1456, 1370, 1240, 1158, 1074, 970, 837, 745, 726 cm^{-1}. **MP**: 86–90 ^{o}C. **$[\alpha]_D^{25}$** +25^{o}, c = 0.30 in DCM

(3a*R*,8a*R*)-6-(benzofuran-2-yl)-4,4,8,8-tetraethyl-tetrahydro-2,2-dimethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.62



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.54 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.31 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.22 (td, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.14 (s, 1H), 4.61 (dd, *J* = 9.2 Hz, 2.8 Hz, 1H), 4.29 (d, *J* = 9.2 Hz, 1H), 2.32-2.24 (m, 1H), 2.03-1.82 (m, 5H), 1.75-1.55 (m, 2H), 1.39 (s,6H), 1.03-0.94 (m, 12H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 159.5 (d, *J* = 15.4 Hz), 157.3 (d, *J* = 4.4 Hz), 127.3 (d, *J* = 4.4 Hz), 125.2, 122.7, 121.7, 112.9 (d, *J* = 19.8 Hz), 111.9, 109.2, 81.1 (d, *J* = 17.7 Hz), 80.1 (d, *J* = 2.7 Hz), 79.8 (d, *J* = 2.7 Hz), 79.5(d, *J* = 4.4 Hz), 31.6 (d, *J* = 5.0 Hz), 30.0 (d, *J* = 3.9 Hz), 27.3, 27.0, 25.6, 23.5 (d, *J* = 9.9 Hz), 8.0 (d, *J* = 1.7 Hz), 7.6, 7.2, 7.1 (d, *J* = 2.2 Hz). **^{31}P NMR** (121.5 MHz, $CDCl_3$): δ 136.8. **HRMS** calcd for $C_{23}H_{34}O_5P$(M+1): 421.2144, Found: 421.2144. **FTIR** (neat): 2971, 2938, 2881, 1461, 1378, 1355, 1275, 1175, 1134, 1081, 1020, 974, 935, 840, 745, 724 cm^{-1}. **MP**: 54-56 ^{o}C. **$[\alpha]_D^{25}$** +34.4, c = 1.13 in DCM

(4*R*,5*R*)-diisopropyl- 2,2-dimethyl-1,3-dioxolane-4,5-dipropan-2-ol

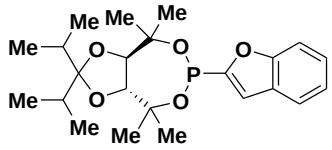


To (1*R*,2*R*)-2,3-bis-trimethylsilanyloxy-succinic acid dimethyl ester (12.2 g, 38 mmol, 100 mol%) and 2,4-dimethylpentan-3-one (5.4 mL, 38 mmol, 100 mol%) was added freshly distilled TMSOTf (6.8 mL, 38 mmol, 100 mol%) and TfOH (0.4 mL, 4.5 mmol, 12 mol%) and the reaction was stirred at 60 ^{o}C for 48 hours. Et_3N (5.3 mL, 38 mmol, 100 mol%) was added, followed by saturated aqueous $NaHCO_3$ solution (20 mL), and the mixture was extracted with ether (3 X 20 mL), washed with brine and dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the crude (1*R*,2*R*)-dimethyl 4,4-diisopropylcyclopentane-1,2-dicarboxylate (10.4 g, 38 mmol, 100 mol%), which was sufficiently pure to be used directly in the next step, was dissolved in ether (0.4 M), MeMgBr (1.4 M, 200 mL, 280 mmol, 740 mol%)

was added over 1hour, and the mixture was stirred for 10 h at 25 ^{o}C, at which time saturated aqueous KH_2PO_4 solution was added and the mixture was extracted wtih EtOAc (3 X 40 mL), washed with brine, dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The resulting crude material was filtered through a short plug of silica gel to give the title compound in 94% yield over 2 steps (9.8 g, 35.7 mmol).

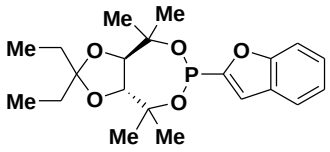
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 (s, 2H), 3.60 (s, 2H), 2.04 (sep, *J* = 6.8 Hz, 2H), 1.36 (s, 6H), 1.28 (s, 6H), 0.94 (d, *J* = 6.8 Hz, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 111.9, 82.6, 70.7, 34.5, 29.4, 23.5, 18.1, 17.6. **HRMS** calcd for $C_{15}H_{31}O_4$ (M+1): 275.2222, Found: 275.2225. **FTIR** (neat): 3257, 2971, 1471, 1384, 1366, 1182, 1069, 954, 948 cm^{-1}. **MP**: 90-92 ^{o}C.

(3a*R*,8a*R*)-6-(benzofuran-2-yl)-tetrahydro-2,2-diisopropyl-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.65



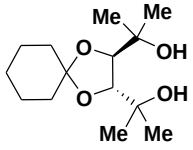
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (bd, *J* = 7.5 Hz, 1H), 7.57 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.33 (td, *J* = 7.2, 1.4 Hz, 1H), 7.26 – 7.20 (m, 2H), 4.40 (dd, *J* = 9.6, 3.1 Hz, 1H), 3.98 (d, *J* = 9.6 Hz, 1H), 2.18 – 2.05 (m, 2H), 1.65 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H), 1.46 (s, 3H), 1.04 – 0.99 (m, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.3 (d, *J* = 13.8 Hz), 157.3 (d, *J* = 3.9 Hz), 127.2 (d, *J* = 5.4 Hz), 125.5, 122.8, 121.8, 114.8, 114.2 (d, *J* = 25.4 Hz), 112.0, 82.6 (d, *J* = 4.6 Hz), 82.1 (d, *J* = 21.5 Hz), 77.4 (d, *J* = 6.2 Hz), 77.2 (d, *J* = 6.2 Hz), 34.6 (d, *J* = 3.8 Hz), 31.6, 30.2 (d, *J* = 1.9 Hz), 29.5 (d, *J* = 2.3 Hz), 25.2, 24.0, 22.6, 20.8 (d, *J* = 11.5 Hz), 18.1 (d, *J* = 5.4 Hz), 17.6 (d, *J* = 6.2 Hz). **^{31}P NMR** (121.5 MHz, $CDCl_3$): δ 135.7. **HRMS** calcd for $C_{23}H_{34}O_5P$ (M+1): 421.2144, Found: 421.2147. **FTIR** (neat): 2974, 2939, 2895, 1471, 1445, 1380, 1235, 1179, 1147, 1113, 1080, 1019, 797, 753, 649 cm^{-1}. **MP**: 102-105 ^{o}C. **$[\alpha]_D^{25}$** +3.0, c = 1.2 in DCM

(3a*R*,8a*R*)-6-(benzofuran-2-yl)-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.64



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.55, (ddd, *J* = 8.4, 1.8, 0.9 Hz, 1H), 7.32 (ddd, *J* = 8.4, 7.2, 1.3 Hz,1H), 7.22 (ddd, *J* = 7.9, 7.9, 1.0 Hz, 1H), 7.18 (dd, *J* = 1.3, 1.3 Hz, 1H), 4.44 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.98 (d, *J* = 9.4 Hz, 1H), 1.67 (q, *J* = 7.5 Hz, 2H), 1.66 (q, *J* = 7.5 Hz, 2H) 1.60 (s, 6H), 1.49 (s, 3H), 1.40 (s, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.3 (d, *J* = 13.4 Hz), 157.3 (d, *J* = 3.7 Hz), 127.2 (d, *J* = 5.2 Hz), 125.5, 122.9, 121.8, 114.2 (d, *J* = 24.7 Hz), 113.2, 112.0, 82.6 (d, *J* = 4.5 Hz), 82.1 (d, *J* = 22.4 Hz), 77.2 (d, *J* = 6.7 Hz, 2C), 30.2 (d, *J* = 10.4 Hz, 2C), 30.1 (d, *J* = 2.9 Hz), 29.3 (d, *J* = 2.9 Hz), 23.5, 20.2 (d, *J* = 10.5 Hz), 8.1 (d, *J* = 2.2 Hz, 2C). **^{31}P NMR** (121 MHz, $CDCl_3$): δ 136.6. **HRMS** calcd for $C_{21}H_{30}O_5P$ (M+1): 393.1830, Found: 393.1831. **FTIR** (neat): 2976, 2939, 2881, 1535, 1463, 1449, 1383, 1368, 1253, 1157, 1078, 1008, 970, 938 cm^{-1}. **$[\alpha]_D^{25}$** +196, c = 1.0 in DCM.

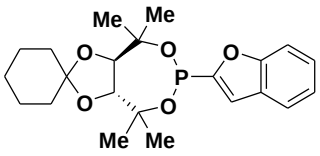
2-[3-(1-Hydroxy-1-methyl-ethyl)-1,4-dioxa-spiro[4.5]dec-2-yl]-propan-2-ol



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 2H), 3.59 (s, 2H), 1.59–1.57 (m, 8H), 1.40–1.35 (m, 2H), 1.33 (s, 6H), 1.26 (s, 6H). **^{13}C NMR** (100.5 MHz, $CDCl_3$) δ 108.0, 82.2, 70.6, 36.8, 29.1, 25.1, 23.9. **HRMS** calcd for $C_{14}H_{27}O_4$ (M+1): 259.1909, Found: 259.1915.

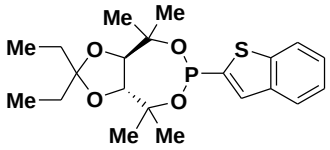
FTIR (neat): 3224(br), 2973, 2932, 2897, 1439, 1381, 1365, 1276, 1192, 1161, 1125, 1144, 1091, 1057, 949, 906 cm^{-1}. **MP**: 134-136 ^{o}C. **$[\alpha]_D^{25}$** -8.9^{o}, c = 0.79 in DCM

(3a*R*,8a*R*)-6-(benzofuran-2-yl)-2,2-cyclohexyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.66



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.54 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.31 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.22 (td, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.14 (s, 1H), 4.48 (dd, *J* = 11.5 Hz, 5 Hz, 1H), 4.00 (d, *J* = 11.5 Hz, 1H), 1.62 – 1.55 (m, 16H), 1.37 (s, 6H). **^{13}C NMR** (100.5 MHz, $CDCl_3$): δ 158.2 (d, *J* = 13.8 Hz), 157.3 (d, *J* = 3.8 Hz), 127.2 (d, *J* = 5.3 Hz), 125.5, 122.8, 121.7, 114.1 (d, *J* = 23.8 Hz), 111.9, 110.2, 82.0 (d, *J* = 3.8 Hz), 80.6, 81.4, 77.0 (d, *J* = 6.1 Hz), 76.9 (d, *J* = 6.1 Hz), 36.7 (d, *J* = 9.2 Hz), 30.0 (d, *J* = 3.1 Hz), 29.7, 29.1 (d, *J* = 2.3 Hz), 25.0, 23.8, 23.2, 19.9 (d, *J* = 9.9 Hz). **^{31}P NMR** (121.5 MHz, $CDCl_3$): δ 135.6. **HRMS** calcd for $C_{22}H_{30}O_5P$(M+1): 405.1831, Found: 405.1833. **FTIR** (neat): 2933, 2856, 1445, 1384, 1368, 1278, 1253, 1159, 1144, 1122, 1090, 1059, 1009, 970, 945, 927, 826, 793, 743 cm^{-1}. **MP**: 90-92 ^{o}C. **$[\alpha]_D^{25}$** -52.7, c = 0.97 in DCM.

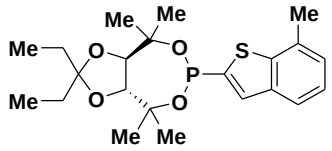
(3a*R*,8a*R*)-6-(benzo[b]thiophen-2-yl)-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, AP-I



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.84 (m, 1H), 7.81-7.79 (m, 1H), 7.67 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.35-7.32 (m, 2H), 4.44 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.95 (d, *J* = 9.4 Hz, 1H), 1.68-1.64 (m, 4H), 1.58 (s, 6H), 1.48 (s, 3H), 1.38, (s, 3H), 0.95-0.90 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 144.4 (d, *J* = 26.2 Hz), 142.8, 139.6 (d, *J* = 10.47 Hz), 130.4 (d, *J* = 35.9), 125.3, 124.4, 124.3 (d, *J* = 23.2 Hz), 122.5, 113.1, 82.6 (d, *J* = 3.7 Hz), 82.0, 77.2, 77.1, 30.2 (d, *J* = 4.4 Hz, 2C) 29.3 (d, *J* = 2.2 Hz), 23.5, 20.4, 20.3, 8.1 (2C). **^{31}P NMR** (162 MHz, $CDCl_3$): δ 143.2. **HRMS** calcd for $C_{21}H_{30}O_4PS$ (M+1): 409.1602, Found: 409.1602. **FTIR** (neat) 3400, 2973, 2939, 1503, 1461,

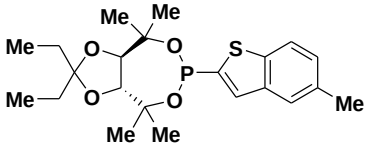
1373, 1227, 1177, 1157, 1075, 1035, 1006, 969 cm^{-1}. **MP**: 66-69 °C. $[\alpha]_D^{25}$ +195, c = 1.0 in DCM

(3a*R*,8a*R*)-2,2-diethyl-4,4,8,8-tetramethyl-6-(7-methylbenzo[b]thiophen-2-yl)-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, AP-II



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.15-7.12 (m, 1H), 4.45 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 2.56 (s, 3H), 1.70-1.63 (m, 4H), 1.58 (s, 6H), 1.49 (s, 3H), 1.39, (s, 3H), 0.95-0.90 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 143.6 (d, *J* = 26.0 Hz), 143.0, 139.4 (d, *J* = 10.4 Hz), 132.1, 131.2 (d, *J* = 36.5 Hz), 125.4, 124.6, 122.0, 113.0, 82.6 (d, *J* = 3.7 Hz), 82.2, 82.0, 77.0 (d, *J* = 6.0 Hz), 30.3 (d, *J* = 3.0 Hz), 30.2 (d, *J* = 2.9 Hz), 29.3 (d, *J* = 2.9 Hz), 23.5, 22.6, 20.3 (d, *J* = 10.4 Hz), 20.3, 8.1 (2C). **^{31}P NMR** (121.5 MHz, $CDCl_3$): δ 142.0. **HRMS** calcd for $C_{22}H_{31}O_4PS$ (M+1): 423.159, Found: 423.1755. **FTIR** (neat) 2975, 2938, 1463, 1383, 1367, 1157, 1079, 1061, 970, 939 cm^{-1}. $[\alpha]_D^{25}$ -7.6, c = 1.2 in DCM

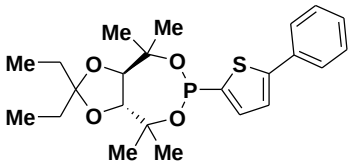
(3a*R*,8a*R*)-2,2-diethyl-4,4,8,8-tetramethyl-6-(5-methylbenzo[b]thiophen-2-yl)-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, AP-III



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, 1H), 7.60-7.58 (m, 2H), 7.17 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 4.44 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 2.45 (s, 3H), 1.70-1.64 (m, 4H), 1.57 (s, 6H), 1.47 (s, 3H), 1.37, (s, 3H), 0.95-0.90 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 144.3 (d, *J* = 26.0 Hz), 140.0 (d, *J* = 16.3 Hz), 130.0 (d, *J* = 5.2 Hz), 133.8, 130.1 (d, *J* = 36.5 Hz), 127.2, 124.1, 122.1, 113.0, 82.6 (d, *J* = 3.8 Hz), 82.2, 82.0, 77.0 (d, *J* = 5.2 Hz), 30.2, 30.1, 29.3 (d, *J* = 3.0 Hz), 23.5, 21.3, 20.4, 20.3, 8.1 (2C). **^{31}P NMR** (121.5 MHz, $CDCl_3$): δ 142.1.

HRMS calcd for $C_{22}H_{32}O_4PS$ (M+1): 423.1759, Found: 423.1764. **FTIR** (neat) 2975, 2937, 1463, 1383, 1368, 1157, 1079, 993, 970, 940 cm^{-1}. **MP**: 92-94 °C. $[\alpha]_D^{25}$ -10.54, c = 1.3 in DCM

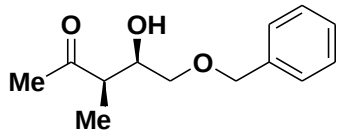
(3a*R*,8a*R*)-2,2-diethyl-4,4,8,8-tetramethyl-6-(5-phenylthiophen-2-yl)-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine, AP-IV



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (ddd, *J* = 7.6, 2.0, 0.8 Hz, 2H), 7.41-7.34 (m, 3H), 7.30 (ddd, *J* = 7.2, 1.2, 1.2 Hz, 1H), 7.27 (dd, *J* = 3.5, 1.6 Hz, 1H), 4.43 (dd, *J* = 9.4, 3.3Hz, 1H), 3.94 (d, *J* = 9.4Hz, 1H), 1.66 (q, *J* = 2.9Hz, 2H), 1.66 (q, *J* = 3.5Hz, 2H), 1.56 (s, 6H), 1.47 (s, 3H), 1.37 (s, 3H), 0.93 (t, *J* = 7.4Hz, 3H), 0.92 (t, *J* = 7.4Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 150.8 (d, *J* = 2.2Hz), 142.8, 142.6, 134.7, 134.4, 134.3, 129.1, 128.2, 126.5, 123.6 (d, *J* = 9.7Hz), 113.2, 82.9 (d, *J* = 3.7Hz), 82.3 (d, *J* = 21.7Hz), 77.1 (d, 2.2Hz), 77.1, 30.5 (2C), 30.5 (d, *J* = 5.2Hz), 29.6 (d, *J* = 3.0Hz), 23.8, 20.6 (d, *J* = 10.5Hz), 8.4 (2C). **^{31}P NMR** (121.5) MHz, $CDCl_3$): δ 140.8. **HRMS** calcd for $C_{23}H_{32}O_4PS$ (M+1): 435.1756, Found: 435.1759. **FTIR** (neat): 3062, 2976, 2940, 2881, 1772, 1715, 1601, 1528, 1490, 1463, 1437, 1383, 1368, 1205, 1174, 1157 cm^{-1}. **MP**: 93-96 °C. $[\alpha]_D^{25}$ -3°, c = 1.0 in DCM

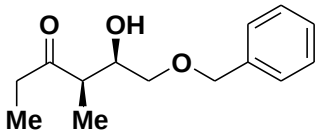
2.6.5 Spectroscopic Data for the Aldol Products

(3*R*,4*R*)-5-(benzyloxy)-4-hydroxy-3-methylpentan-2-one, 2.42



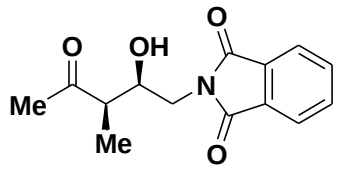
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.36 (m, 5H), 4.51 (s, 2H), 4.09-4.10 (m, 1H), 3.41-3.53 (m, 2H), 2.90 (d, *J* = 2.7 Hz, 1H), 2.61-2.77 (dq, *J* = 7.2, 5.1 Hz, 1H), 2.16 (s, 3H), 1.14 (d, *J* = 7.2 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.2, 137.7, 128.3, 127.7, 127.6, 73.3, 71.6, 70.2, 48.6, 29.2, 11.0.**HRMS** Calcd for $C_{13}H_{18}O_3$ (M+1): 223.1334, Found: 223.1330.**FTIR** (neat): 3439, 3031, 2920, 2867, 1704, 1455, 1360, 1252, 1207, 1181, 1094, 1028, 957, 916, 739, 699 cm^{-1}. **HPLC**: (Chiralpak AS-H column, 10% *i*-PrOH/ hexanes, 0.8 mL/ min, 254 nm), t_{major} = 9.7 min, t_{minor} = 11.3 min); ee = 91%. $[\alpha]_D^{25}$ -5°, c = 1.0 in DCM

(4*R*,5*R*)-6-(benzyloxy)-5-hydroxy-4-methylhexan-3-one, 2.42a



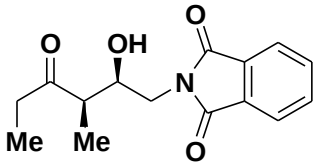
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.36 (m, 5H), 4.50 (s, 2H), 4.05 (q, *J* = 5.4, 1H), 3.40-3.47 (m, 2H), 2.93 (s, 1H), 2.73-2.80 (dq, *J* = 5.1, 7.2 Hz, 1H), 2.40-2.57 (m, 2H), 1.12 (d, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.4, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.9, 137.7, 128.3, 127.7, 73.3, 71.6, 70.5, 47.6, 35.2, 11.5, 7.4. **HRMS** Calcd for $C_{14}H_{20}O_3$ (M+1): 237.1491, Found: 237.1488. **FTIR** (neat): 3502, 3064, 3031, 2977, 2938, 1705, 1497, 1455, 1410, 1376, 1250, 1208, 1099, 1028, 976, 915, 738, 699 cm^{-1}. **HPLC**: (Chiralpak OD-H column, 5% *i*-PrOH/ hexanes, 0.5 mL/ min, 254 nm), t_{minor} = 20.8 min, t_{major} = 26.4 min); ee = 88%.

2-((2*R*,3*R*)-2-hydroxy-3-methyl-4-oxopentyl)isoindoline-1,3-dione, 2.56



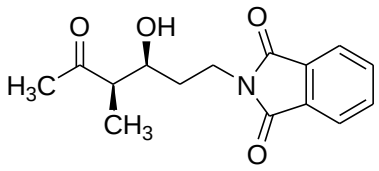
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.84 (m, 2H), 7.74-7.72 (m, 2H), 4.30-4.25 (m, 1H), 3.85 (dd, *J* = 14.2, 7.4 Hz, 1H), 3.75 (dd, *J* = 14.4, 4.4 Hz, 1H), 2.95-2.93 (m, 1H), 2.68 (dq, *J* = 4.2, 7.2 Hz, 1H), 2.23 (s, 3H), 1.29 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.4, 169.0, 134.4, 132.1, 123.7, 69.9, 49.4, 41.7, 29.2, 10.9. **HRMS** Calcd for $C_{14}H_{15}NO_4$ (M+1): 261.1001, Found: 261.1004. **FTIR** (neat): 3435, 3053, 2978, 2935, 2872, 2306, 1640, 1446, 1383, 1351, 1266, 1114, 1076, 896, 743 cm^{-1}. **Mp**: 140-141 ^oC. **HPLC**: (Chiralpak AD-H column, 10% *i*-PrOH/ hexanes, 1 mL/ min, 254 nm), t_{major} = 30.5 min, t_{minor} = 34.7 min); ee = 96%. **$[\alpha]_D^{25}$** +0.6, c = 1.6 in DCM

2-((2*R*,3*R*)-2-hydroxy-3-methyl-4-oxohexyl)isoindoline-1,3-dione, 2.56a



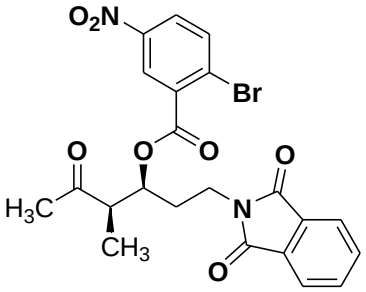
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.83 (m, 2H), 7.76-7.71 (m, 2H), 4.28-4.23 (m, 1H), 3.85 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.73 (dd, *J* = 14.2, 4.6 Hz, 1H), 3.10 (d, *J* = 3.8 Hz, 1H), 2.69 (dq, *J* = 4.3, 7.2 Hz, 1H), 2.60 (dq, *J* = 18.1, 7.2 Hz, 1H), 2.51 (dq, *J* = 18.1, 7.2 Hz, 1H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.8, 168.6, 134.0, 131.8, 123.3, 69.6, 48.2, 41.3, 34.7, 10.9, 7.4. **HRMS** Calcd for $C_{15}H_{17}NO_4$ (M+1): 275.1158, Found: 275.1158. **FTIR** (neat): 3454, 3054, 2986, 2305, 2254, 1773, 1714, 1642, 1422, 1397, 1265, 909, 748 cm^{-1}. **HPLC**: (Chiralpak AD-H column, 4% *i*-PrOH/ hexanes, 1.0 mL/ min, 254 nm), t_{minor} = 91.4 min, t_{major} = 97.1 min); ee = 96%. **$[\alpha]_D^{25}$** +1.4, c = 1.4 in DCM

2-((3S,4R)-3-hydroxy-4-methyl-5-oxohexyl)isoindoline-1,3-dione, 2. 69



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.83 (m, 2H), 7.75-7.71 (m, 2H), 3.93-3.77 (m, 3H), 3.20 (d, *J* = 3.8 Hz, 1H), 2.61 (dq, *J* = 3.8, 7.2 Hz, 1H), 2.19 (s, 3H), 1.85-1.67 (m, 2H), 1.17 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.8, 168.6, 134.0, 131.9, 123.2, 68.4, 51.1, 34.8, 33.0, 29.3, 10.5. **HRMS**: Calcd [M] for $C_{15}H_{17}NO_4$: 275.1158; Found: 275.1156. **FTIR** (film): 3469, 3054, 2986, 2305, 2254, 1771, 1710, 1468, 1397, 1372, 1265, 1177, 951, 910, 741 cm^{-1}. **HPLC**: (Chiralpak AD-H column, 5% *i*-PrOH/ hexanes, 1.0 mL/ min, 220 nm), t_{minor} = 57.2 min, t_{major} = 66.5 min); ee = 89%.

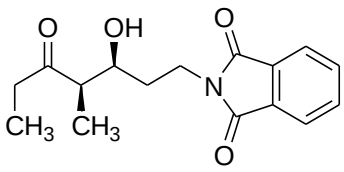
(3S,4R)-1-(1,3-dioxoisoindolin-2-yl)-4-methyl-5-oxohexan-3-yl 2-bromo-5-nitrobenzoate, 2.69p



To a solution of 2-((3S,4R)-3-hydroxy-4-methyl-5-oxohexyl)isoindoline-1,3-dione (100 mg, 0.36 mmol, 100 mol%) and 2-bromo-4-nitrobenzoyl chloride (133 mg, 0.50 mmol, 140 mol%) in 1 mL of DCM at ambient temperature, triethylamine (0.15 mL, 1.1 mmol, 300 mol%) was added and the solution was allowed to stir for 10 hours at ambient temperature. The mixture was diluted with 10 mL DCM, and the organic layer was washed 2 X 10 mL water, and then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure, followed by purification by silica gel chromatography gave the title compound in 87% yield (158 mg, 0.31 mmol).

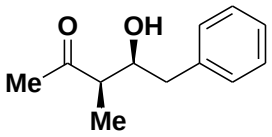
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 2.7 Hz, 1H), 8.15 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.54 (q, *J* = 6.4 Hz, 1H), 3.93–3.77 (m, 2H), 3.07–3.04 (m, 1H), 2.27 (s, 3H), 2.18 (q, *J* = 6.7 Hz, 2H), 1.23 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 208.5, 168.1, 163.7, 146.7, 135.6, 134.1, 133.3, 131.9, 128.9, 126.6, 126.3, 123.3, 73.8, 49.6, 34.5, 30.6, 29.5, 11.4. **HRMS**: Calcd [M+1] for $C_{22}H_{20}BrN_2O_7$: 503.0454; Found: 503.0455. **FTIR** (film): 2947, 2356, 1713, 1606, 1530, 1347, 1269, 1125, 1032, 720 cm^{-1}. **HPLC**: (Chiralpak AS-H column, 10% *i*-PrOH/ hexanes, 1.0 mL/ min, 254 nm), t_{minor} = 47.8 min, t_{major} = 58.4 min).

2-((3S,4R)-3-hydroxy-4-methyl-5-oxoheptyl)isoindoline-1,3-dione, 2.69a



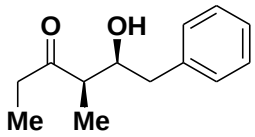
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.81 (m, 2H), 7.75-7.71 (m, 2H), 3.91-3.71 (m, 3H), 3.34 (d, *J* = 4.1 Hz, 1H), 2.64 (dq, *J* = 4.4, 7.2 Hz, 1H), 2.57 (dq, *J* = 18.1, 7.3 Hz, 1H), 2.49 (dq, *J* = 18.1, 7.2 Hz, 1H), 1.84-1.67 (m, 2H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 215.5, 138.6, 133.9, 131.9, 123.2, 68.6, 50.1, 35.3, 34.8, 33.0, 11.0, 7.4. **HRMS**: Calcd [M] for $C_{16}H_{19}NO_4$: 289.1314; Found: 289.1316. **FTIR** (film): 3466, 3054, 2985, 2305, 2254, 1771, 1710, 1468, 1397, 1265, 952, 911, 741 cm^{-1}. **HPLC**: (Chiralpak AS-H column, 5% *i*-PrOH/ hexanes, 0.5 mL/ min, 220 nm), t_{minor} = 78.5 min, t_{major} = 91.8 min); ee = 92%. **$[\alpha]_D^{25}$** -5.0°, c = 1.0 in DCM

3*R*,4*S*)-4-hydroxy-3-methyl-5-phenylpentan-2-one, 2.70



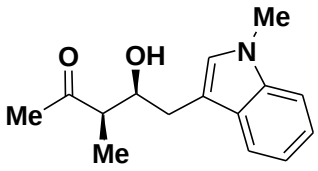
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, *J* = 7.2 Hz, 3H), 2.16 (s, 3H), 2.56 (dq, *J* = 3.4, 7.2 Hz, 1H), 2.67-2.68 (br, 1H), 2.69 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.79 (dd, *J* = 13.7, 7.9 Hz, 1H), 4.18-4.22 (m, 1H), 7.20-7.26 (m, 3H), 7.28-7.33 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 213.4, 138.1, 129.2, 128.5, 126.5, 72.0, 49.9, 40.3, 29.1, 9.9. **HRMS** Calcd for $C_{12}H_{16}O_2$ (M+1): 193.1229, Found: 193.1227. **FTIR** (neat): 3501, 3054, 2985, 2685, 2306, 1701, 1603, 1496, 1455, 1358, 1266, 1171, 1031, 909, 896, 734 cm^{-1}. **HPLC**: (Chiralpak OJ-H column, 7% *i*-PrOH/ hexanes, 0.8 mL/ min, 254 nm), t_{minor} = 15.0 min, t_{major} = 16.7 min); ee = 90%.

(4*R*,5*S*)-5-hydroxy-4-methyl-6-phenylhexan-3-one, 2.70a



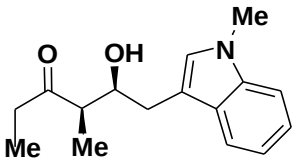
^{1}H NMR (400 MH, $CDCl_3$): δ 7.33-7.20 (m, 5H), 4.19-4.14 (m, 1H), 2.79 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.72-2.72 (m, 1H), 2.68 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.59 (dq, *J* = 3.4, 7.2 Hz, 1H), 2.52 (dq, *J* = 18.1, 7.3 Hz, 1H), 2.43 (dq, *J* = 18.1, 7.3 Hz, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 216.1, 138.2, 129.1, 128.4, 126.4, 72.2, 48.8, 40.3, 35.0, 10.3, 7.5. **HRMS** Calcd for $C_{13}H_{18}O_2$ (M+1): 207.1385, Found: 207.1385. **FTIR** (neat): 3943, 3512, 3054, 2984, 2941, 2685, 2305, 1698, 1604, 1496, 1455, 1421, 1379, 1265, 1110, 1030, 976, 896, 737 cm^{-1}. **HPLC**: (Chiralpak OD-H column, 2% *i*-PrOH/ hexanes, 1.0 mL/ min, 254 nm), t_{minor} = 12.6 min, t_{major} = 14.6 min); ee = 90%.

(3*R*,4*S*)-4-hydroxy-3-methyl-5-(1-methyl-1H-indol-3-yl)pentan-2-one, 2.71



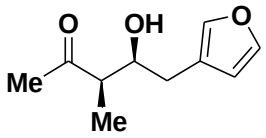
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (ddd, *J* = 7.9, 1.9, 1.2 Hz, 1H), 7.28 (ddd, *J* = 8.2, 1.8, 1.0 Hz, 1H), 7.22 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 7.10 (ddd, *J* = 7.9, 6.9, 1.2 Hz, 1H), 6.90 (s, 1H), 4.26 (m, 1H), 3.72 (s, 3H), 2.88 (s, 1H), 2.86 (dd, *J* = 1.6, 0.6, 1H), 2.62 (qd, *J* = 7.3, 4.0, 1H), 2.57 (m, 1H), 2.14 (s, 3H), 1.23 (d, *J* = 7.2, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 213.5, 137.4, 128.1, 127.7, 122.0, 119.2(2C), 110.6, 109.6, 71.4, 50.6, 32.9, 30.4, 29.5, 10.5. **HRMS** calcd for $C_{15}H_{20}NO_2$ (M+1): 246.1494, Found: 246.1491. **FTIR** (neat): 3446, 3053, 2935, 1704, 1615, 1472, 1425, 1375, 1357, 1328, 1250, 1173, 1155, 1126, 1091, 1070, 1032, 1012, 981 cm^{-1}. **HPLC**: (Chiralpak OD-H column, 5% *i*-PrOH/ hexanes, 0.5 mL/ min, 254 nm), t_{minor} = 67.2 min, t_{major} = 71.4 min); ee = 86%.

(4*R*,5*S*)-5-hydroxy-4-methyl-6-(1-methyl-1H-indol-3-yl)hexan-3-one, 2.71a



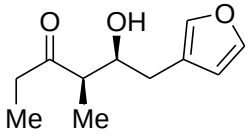
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.28 (m, 1H), 7.22 (m, 1H), 7.10 (m, 1H), 6.90 (s, 1H), 4.24 (ddd, *J* = 10.4, 6.3, 4.2 Hz, 1H), 3.72 (s, 3H), 2.88 (s, 1H), 2.86 (d, *J* = 3.2 Hz, 1H), 2.65 (m, 2H), 2.47 (m, 2H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 216.3, 137.4, 128.2, 127.7, 122.0, 119.3, 119.2, 110.7, 109.6, 71.7, 49.6, 35.4, 32.9, 30.4, 11.0, 7.8. **HRMS** calcd for $C_{16}H_{22}NO_2$ (M+1): 260.1651, Found: 260.1649. **FTIR** (neat): 3474, 3054, 2975, 2036, 1704, 1615, 1552, 1473, 1425, 1376, 1328, 1250, 1155, 1132, 1061, 1012, 974, 741 cm^{-1}. **HPLC**: (Chiralpak OJ-H column, 10% *i*-PrOH/ hexanes, 1 mL/ min, 254 nm), t_{minor} = 17.5 min, t_{major} = 20.6 min); ee = 90%.

(3*R*,4*S*)-5-(furan-3-yl)-4-hydroxy-3-methylpentan-2-one, 2.72



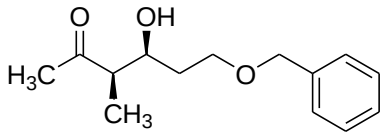
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (s, 1H), 7.31 (s, 1H), 6.32 (s, 1H), 4.15-4.11 (m, 1H), 2.65-2.50 (m, 4H), 2.19 (s, 3H), 1.61 (dd, *J* = 7.6 Hz, 0.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 213.4, 143.1, 140.0, 120.9, 111.1, 70.9, 49.9, 29.5, 29.1, 9.8. **HRMS** calcd for $C_{10}H_{15}O_3$ (M+1): 183.1021, Found: 183.1025. **FTIR** (neat): 3445, 2922, 1699, 1457, 1360, 1157, 1067, 1024, 874, 787, 734, 601 cm^{-1}. **HPLC**: (Chiralpak AD-H column, 2% *i*-PrOH/ hexanes, 1 mL/ min, 230 nm), t_{major} = 12.3 min, t_{minor} = 13.9 min); ee = 87%.

(4*R*,5*S*)-6-(furan-3-yl)-5-hydroxy-4-methylhexan-3-one, 2.72a



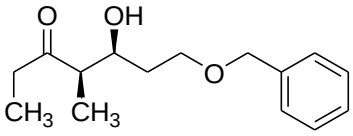
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–73.7 (m, 1H), 7.31–7.29 (m, 1H), 6.32–6.30 (m, 1H), 4.11–4.06 (m, 1H), 2.88–2.73 (bs, 1H), 2.66–2.42 (m, 5H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 216.2, 143.1, 140.1, 121.0, 111.1, 71.1, 48.8, 35.2, 29.5, 10.3, 7.6. **HRMS** calcd for $C_{11}H_{17}O_3$ (M+1): 197.1178, Found: 197.1180. **FTIR** (neat): 3441, 2977, 2938, 1709, 1502, 1461, 1378, 1157, 1109, 1502, 1461, 1378, 1157, 1109, 1024, 976, 874, 786 cm^{-1}. **HPLC**: (Chiralpak AD-H column, 5% *i*-PrOH/ hexanes, 1 mL/ min, 230 nm), t_{minor} = 11.6 min, t_{major} = 13.6 min); ee = 88%.

(3R,4S)-6-(benzyloxy)-4-hydroxy-3-methylhexan-2-one, 2.74



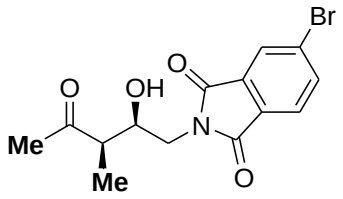
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 4.51 (s, 2H), 4.13-4.10 (m, 1H), 3.71-3.60 (m, 2H), 3.28 (d, *J* = 2.1, 1 H), 2.66-2.57 (m, 1H), 2.18 (s, 3H), 1.82-1.73 (m, 1H), 1.68-1.61 (m, 1H), 1.14 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.8, 137.8, 128.3, 127.6, 127.5, 73.2, 70.5, 68.5, 51.5, 33.6, 29.3, 10.6. **HRMS** Calcd [M+1] for $C_{14}H_{20}O_3$: 237.1491, Found: 237.1496. **FTIR** (film): 3433, 3031, 2924, 2868, 1701, 1455, 1362, 1207, 1181, 1098, 1028, 737, 699 cm^{-1}. **HPLC**: (Chiralpak AS-H column, 10% *i*-PrOH/ hexanes, 0.8 mL/ min, 254 nm), t_{major} = 9.6 min, t_{minor} = 13.8 min); ee = 88%.

(4R,5S)-7-(benzyloxy)-5-hydroxy-4-methylheptan-3-one, 2.74a



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.36 (m, 5H), 4.5 (s, 2H), 4.06-4.09 (m, 1H), 3.60-3.70 (m, 2H), 3.35 (s, 1H), 2.58-2.65 (dq, *J* = 4.4, 8.2 Hz, 1H), 2.45-2.56 (dq, *J* = 2.7, 7.2 Hz, 2H), 1.80-1.71 (m, 1H), 1.60-1.67 (m, 1H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 215.5, 137.8, 128.3, 127.6, 127.5, 73.2, 70.6, 68.5, 50.4, 35.3, 33.6, 11.0, 7.5. **HRMS** Calcd [M+1] for $C_{15}H_{22}O_3$: 251.1647; Found: 251.1648. **FTIR** (film): 3501, 2975, 2938, 2876, 1707, 1455, 1411, 1364, 1099, 1028, 975, 739, 699 cm^{-1}. **HPLC**: (Chiralpak AS-H column, 5% *i*-PrOH/ hexanes, 0.5 mL/ min, 254 nm), t_{major} = 44.9 min, t_{minor} = 57.4 min); ee = 92%. **$[\alpha]_D^{25}$** -2.5°, c = 0.82 in DCM

5-bromo-2-((2*R*,3*R*)-2-hydroxy-3-methyl-4-oxopentyl)isoindoline-1,3-dione, 2.75



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99–7.81 (m, 1H), 7.87 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 4.30 – 4.23 (m, 1H), 3.85 (dd, *J* = 14.1, 7.6 Hz, 1H), 3.70 (dd, *J* = 14.1, 4.3 Hz, 1H), 2.92 (d, *J* = 4.3 Hz, 1H), 2.67 (qd, *J* = 7.3, 4.3 Hz, 1H), 2.23 (s, 3H), 1.28 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.2, 167.8, 167.3, 137.1, 133.5, 130.4, 129.1, 126.8, 124.6, 69.3, 49.2, 41.5, 28.9, 10.6. **HRMS** calcd for $C_{14}H_{15}NO_4Br$ (M+1): 340.0184, Found: 340.0186. **FTIR** (neat): 3480, 1774, 1607, 1419, 1392, 1171, 1102, 1039, 743 cm^{-1}. **MP**: 101-102 ^{o}C.

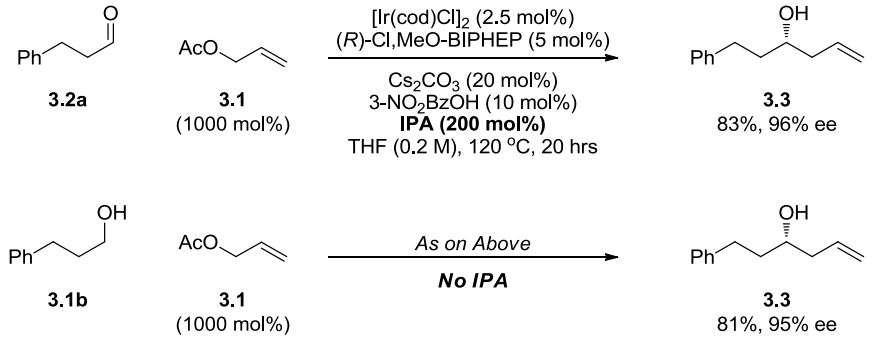
Chapter 3: Application of Iridium-Catalyzed Asymmetric Allylation Reaction under Transfer Hydrogenation Condition: Mono- and Bi-directional Polyol Synthesis from Alcohol Oxidation Level

3.1 Introduction

In Nature's vast collection of polyketide natural products, there exist thousands of compounds incorporating polyacetate derived 1,3-diol or higher 1,3-polyol substructures. While numerous protocols for the synthesis of these ubiquitous structural motifs have been advanced,[55] the allylmetallation of aldehydes has found exceptionally broad use. Carbonyl allylation is one of the most important and widely used carbon-carbon bond forming reactions.[56] The resulting homoallylic alcohol products are amongst the most useful synthetic building blocks in organic chemistry. Additionally the homoallylic alcohols can be transformed to a range of products by functionalization, reduction or oxidation of the double bond. Therefore, tremendous amount of effort has been devoted in the development of asymmetric allylation reactions. For example, asymmetric allylchromation (Nozaki-Hiyama coupling),[57] allyltitanation,[58] allylstannation,[59] allylsilation,[60] and allylboration[61] have been employed in synthetic approaches to 1,3-diols and higher homologues. However, most of these transformations involve stoichiometric use of chirally modified organometallic allylating reagents, which usually require multi-step synthesis. Additionally, the chiral moieties are difficult or impossible to be recovered, so stoichiometric amounts of organometallic byproducts are produced. For instance, Brown's allyl borane [$Ipc_2B(n\text{-}C_3H_5)$, Ipc = isopinocampheyl][62] has found the most extensive use in iterative asymmetric carbonyl allylation, likely due to the low cost of both enantiomers of α-pinene and the fact that excellent levels of reagent-directed diastereoselectivity are observed in the allylation of diverse chiral aldehydes. Despite the effectiveness of $Ipc_2B(n\text{-}C_3H_5)$ in carbonyl allylation, several factors detract from its use, for instance alkaline peroxide is required to release the homoallyl alcohol, which results in the generation of superstoichiometric quantities of isopinocampheol, which frequently complicates product isolation.[63] Additionally, high levels of asymmetric induction often require exceptionally low temperatures (-100 °C), yet $Ipc_2B(n\text{-}C_3H_5)$ is typically generated through the treatment of Ipc_2BOMe with allylmagnesium bromide. In addition only the magnesium salt-free reagent can be used at –100 °C, as the allylborane would otherwise be rendered inactive through the addition of CH_3OMgBr. Although some highly

efficient chiral Lewis acid or base catalyzed asymmetric allylation reactions have been developed, they still rely on the use of stoichiometric amounts of organometallic allyl transfer reagents.

In the course of our studies on hydrogen-mediated reductive carbon-carbon bond formations,[64] we succeeded in developing a byproduct-free carbonyl allylation *via* an iridium catalyzed reductive coupling of 1,1-disubstituted allenes to various aldehydes under the hydrogenation conditions. Later on, we were also successful to discover a very powerful catalytic protocol for enantioselective carbonyl allylation employing allyl acetate as the allyl donor under the conditions of iridium catalyzed transfer hydrogenation.[65] Using isopropanol as a source of hydrogen, allyl acetate is reductively coupled to diverse aldehydes to furnish highly optically enriched homoallylic alcohols. Of greater significance, an alcohol may serve dually as hydrogen donor and carbonyl precursor, enabling carbonyl allylation directly from the alcohol oxidation level. Whereas reductive coupling of allylic alcohols, ethers or carboxylates to carbonyl partners is typically achieved using metallic reductants such as SmI_2, $SnCl_2$, Et_2Zn or Et_3B,[66] transfer hydrogenative carbonyl allylation precludes the use of any stoichiometric metallic reagents (Scheme 3.1).



Scheme 3.1 Iridium catalyzed carbonyl allylation from aldehyde and alcohol oxidation level.

In addition to the step economy associated with bypassing discrete alcohol oxidation and the pre-activation attending stoichiometric use of chiral allylmetal reagents, the ability to perform carbonyl allylation directly from the alcohol oxidation level enables allylation not easily achieved using aldehyde electrophiles. Based on this unique capability, an iterative chain elongation of 1,3-diols to furnish 1,3-polyols were devised. This protocol, which involves

iterative allylation from the alcohol oxidation level, avoids *β*-alkoxy aldehyde intermediates, which are often unstable with respect to elimination.

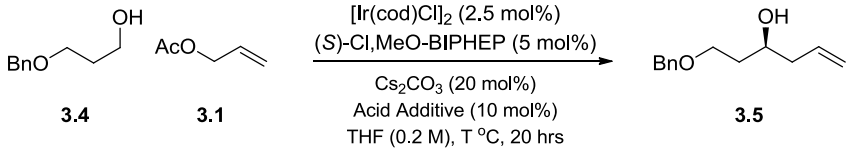
3.2 Part One: Elongation of 1,3-Polyol *via* Iterative Catalyst Directed Allylation Reaction

3.2 .1 Reaction Optimization

Our initial studies focused on the asymmetric allylation of *O*-benzyl propylene glycol **3.4**. Under our previously reported conditions employing the cyclometallated catalyst generated *in situ* from $[Ir(cod)Cl]_2$, (*S*)-Cl,MeO-BIPHEP and 3-nitrobenzoic acid, the coupling of allyl acetate **3.1** (1000 mol%) to **3.4** at 120 ^oC delivers the homoallyl alcohol **3.5** in 82% isolated yield and 94% enantiomeric excess (Table 3.1, entry 1). Lowering the reaction temperature to 100 ^oC slightly enhanced the degree of optical enrichment, but decreased the isolated yield of **3.5** (Table 3.1, entry 2). Interestingly at 120 ^oC, a decrease in the loading of allyl acetate from 10 to 5 equivalents diminished the isolated yield of **3.5** by only 8% (Table 3.1, entries 1 and 3). However, upon a further decrease in the loading of allyl acetate from 5 to 2 equivalents, the isolated yield was unchanged (Table 3.1, entries 3 and 4).

Our discovery that the active catalyst is an *ortho*-cyclometallated iridium *C,O*-benzoate[11b] offered the opportunity to enhance catalyst performance through modification of the benzoate moiety. Consequently, using the iridium *C,O*-benzoate generated *in situ* from $[Ir(cod)Cl]_2$, (*S*)-Cl,MeO-BIPHEP and 4-chloro-3-nitrobenzoic acid, the homoallyl alcohol **3.5** is obtained 88% isolated yield and 95% enantiomeric excess (Table 3.1, entry 5). As a decrease in reaction temperature (100 ^oC) did not improve this result (Table 3.1, entries 6 and 7), the latter conditions employing the catalyst modified by 4-chloro-3-nitrobenzoic acid at 120 ^oC were applied to the iterative homologation of **3.5** to form higher 1,3-polyols.

Table 3.1 Reaction optimization of Ir-catalyzed allylation of *O*-benzyl propylene glycol.



3.4 **3.1** **3.5**

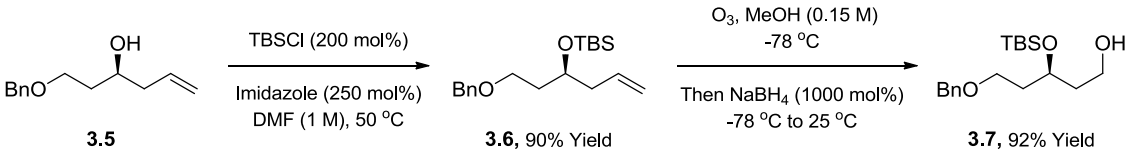
Entry	Acid Additive	Allyl Acetate	T °C	Yield (%)	ee (%)
1	3-NO_2-BzOH	1000 (mol%)	120	82	94
2	3-NO_2-BzOH	1000 (mol%)	100	76	96
3	3-NO_2-BzOH	500 (mol%)	120	74	94
4	3-NO_2-BzOH	200 (mol%)	120	74	95
5	**4-Cl-3-NO_2-BzOH**	**200 (mol%)**	**120**	**88**	**95**
6	4-Cl-3-NO_2-BzOH	200 (mol%)	100	45	95
7[a]	4-Cl-3-NO_2-BzOH	200 (mol%)	100	79	95

[a] Reaction was allowed to proceed for 40 hours.

It is assumed that 4-chloro-3-nitrobenzoic acid derived *ortho*-cyclometallated iridium *C,O*-benzoate catalyst is more reactive due to the electron withdrawing effect of chloro substituent which favor the *C,O*-benzoate by virtue of increase acidity of the iridium hydride intermediate. Also the resulting electron deficient iridium center has increase Lewis acidic character toward starting material alcohol or aldehyde.

3.2.2 Monodirectional Elongation of 1,3-Polyol

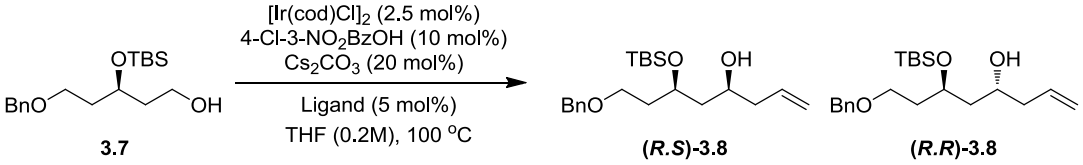
An enantiospecific synthesis of 1,3-polyols[67] *via* iterative carbonyl allylation requires high levels of catalyst-directed diastereoselectivity.[68] Accordingly, homoallyl alcohol **3.5** was converted to the corresponding *tert*-butyldimethylsilyl ether **3.6** in 90% isolated yield, which was subjected to ozonolysis in methanol solvent employing a small quantity of Sudan III as indicator (3-5 drops of a 1.5 mM solution in methanol).[69] Upon complete consumption of **3.6**, which is revealed through the transformation from a pink to a colorless solution, the reaction mixture was treated with sodium borohydride to deliver the alcohol **3.7** in 92% isolated yield. The Sudan III indicator helped to prevent the oxidation of the *O*-benzyl group in **3.7** (Scheme 3.2).



Scheme 3.2 Elaboration of homoallylic alcohol product to homologous 1,3-diol.

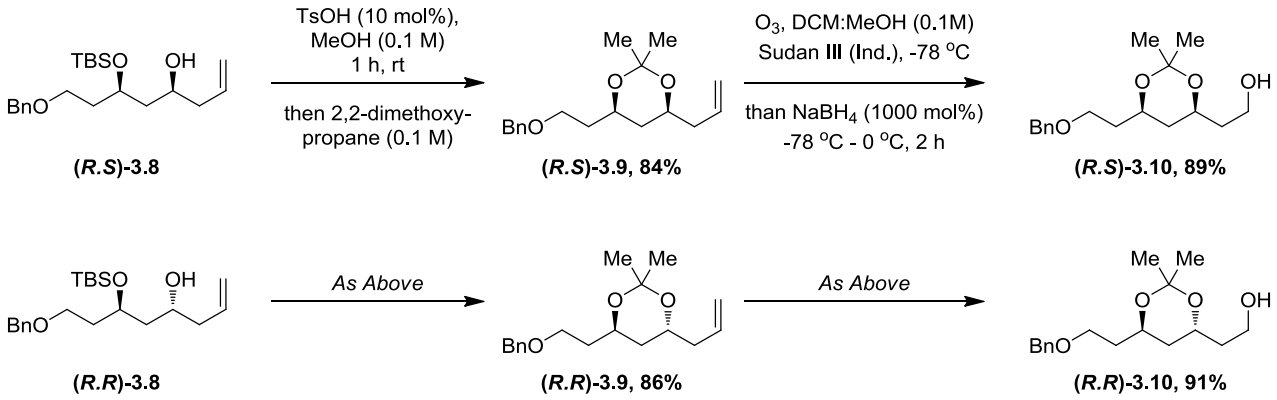
Using previously optimized conditions, the alcohol **3.7** was directly employed to give the product of carbonyl allylation. By using the catalyst modified by (*S*)-Cl,MeO-BIPHEP and 1000 mol% allyl acetate, the product of carbonyl allylation (*R,S*)- **3.8** was obtained in 74% isolated yield as 16:1 ratio of diastereomers. By lowering the allyl acetate loading and extending the reaction time to 40 hours under otherwise identical conditions, (*R,S*)-**3.8** was obtained in 79% isolated yield as a 17:1 ratio of diastereomers. Under these same conditions, but using the catalyst modified by (*R*)-Cl,MeO-BIPHEP, the diastereomeric adduct (*R,R*)-**3.8** was obtained in 79% isolated yield as a 15:1 ratio of diastereomers. It is important to note that upon use of the achiral iridium catalyst ligated BIPHEP, (*R,S*)-**3.8** and (*R,R*)-**3.8** were produced in an equimolar ratio (Table 3.2).

Table 3.2 Catalyst directed diastereoselectivity in the transfer hydrogenative carbonyl allylation and synthesis of higher homologues.



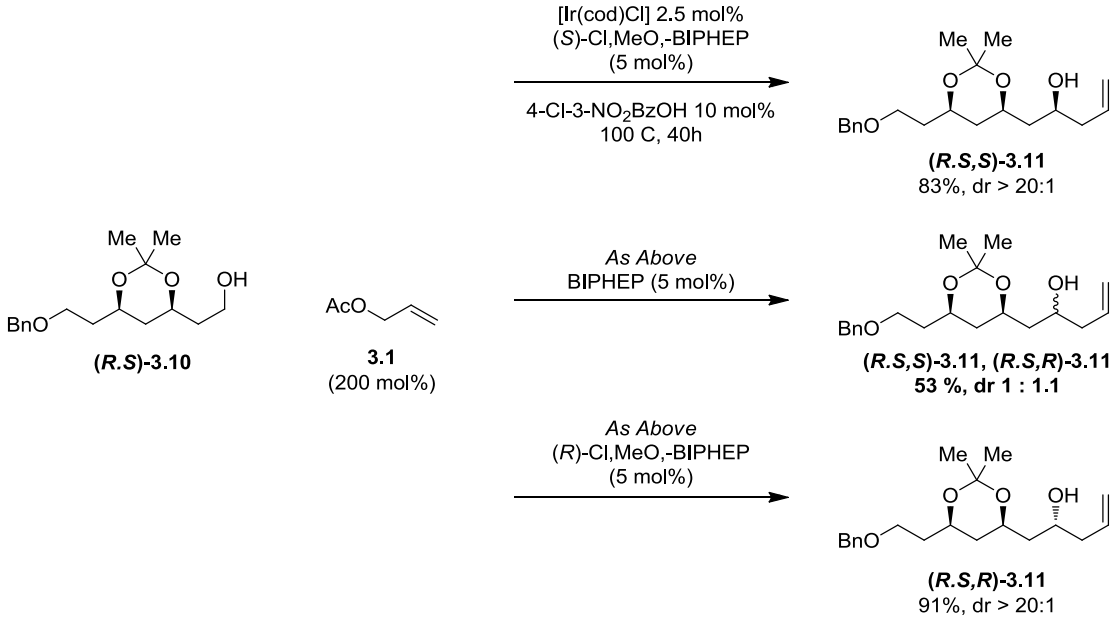
Entry	Allyl Acetate (mol%)	Ligand	Time (hr)	Yield (%)	dr (*syn:anti*)
1	1000	(*S*)-Cl,MeO,-BIPHEP	20	74	16:1
2	500	(*S*)-Cl,MeO,-BIPHEP	20	83	18:1
3	200	(*S*)-Cl,MeO,-BIPHEP	20	55	15:1
4	200	(*S*)-Cl,MeO,-BIPHEP	60	66	15:1
5	**200**	(*S*)-Cl,MeO,-BIPHEP	**40**	**79**	**17:1**
6	200	BIPHEP	40	58	1.1:1
7	**200**	(*R*)-Cl,MeO,-BIPHEP	**40**	**72**	**1:16**

With compounds (*R,S*)-**3.8** and (*R,R*)-**3.8** in hand, the stereoselective synthesis of higher homologues was undertaken. Exposure of (*R,S*)-**3.8** to methanol in the presence of *p*-toluenesulfonic acid (10 mol%) with subsequent introduction of 2,2-dimethoxypropane delivers the diastereomeric acetonide (*R,S*)-**3.9** in one step, as single diastereomers. Ozonolysis of (*R,S*)-**3.9** in accordance with the aforementioned procedure provides (*R,S*)-**3.10**. We were also able to apply the same reaction conditions to convert (*R,R*)-**3.8** to acetonides (*R,R*)-**3.9** and then ozonolysis to primary alcohol (*R,R*)-**3.10** (Scheme 3.3).



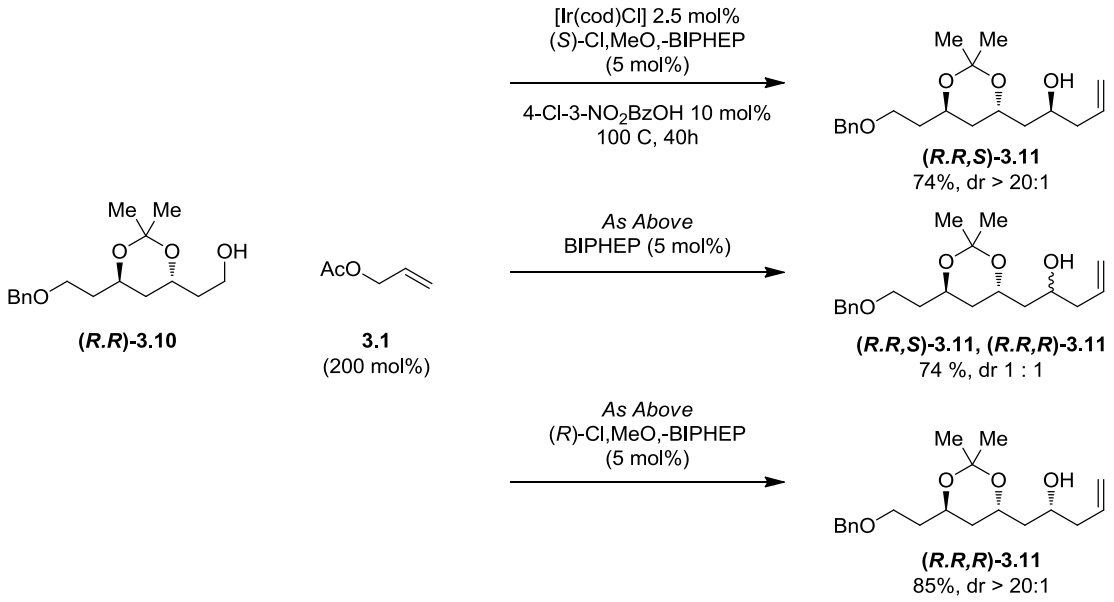
Scheme 3.3 Acetonide protection and ozonolyis of (*R,S*)-**3.8** and (*R,R*)-**3.8**.

With compounds (*R,S*)-**3.10** and (*R,R*)-**3.10,** we have prepared the primary alcohols. Transfer hydrogenative carbonyl allylation of (*R,S*)-**3.10** employing the catalyst modified by (*S*)-Cl,MeO-BIPHEP at 100 ^{o}C delivers the products of carbonyl allylation (*R,S,S*)-**3.11** and the catalyst modified by (*R*)-Cl,MeO-BIPHEP delivers (*R,R,S*)-**3.11**. Again, the allylation was performed with complete diastereoselectivity and the racemic catalyst resulted in a mixture of diastereomers (Scheme 3.4).



Scheme 3.4 Catalyst directed diastereoselectivity in the transfer hydrogenative carbonyl allylation of (*R*,*S*)-**3.10**.

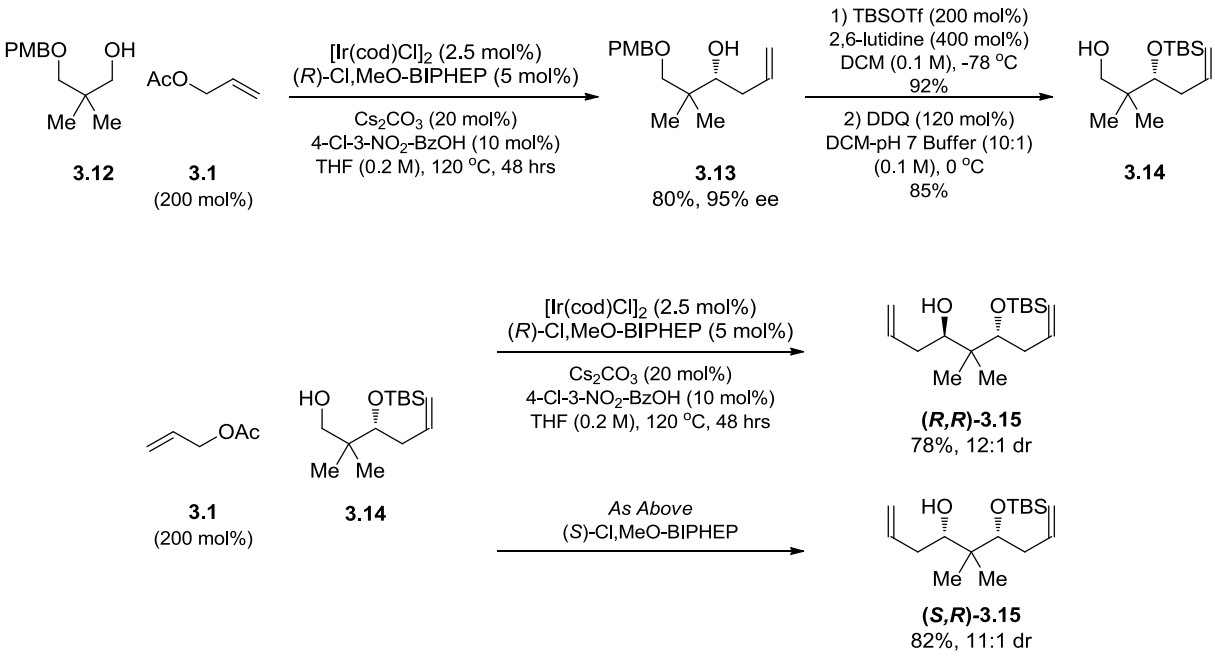
Likewise, using the enantiomeric catalyst modified by (*S*)-Cl,MeO-BIPHEP or (*R*)-Cl,MeO-BIPHEP, (*R*,*R*)-**3.10** were transformed to homoallylic alcohols (*R*,*R*,*S*)-**3.11** and (*R*,*R*,*R*)-**3.11**, respectively. In each case, the minor diastereomer could not be detected by ^{1}H NMR analysis. Upon use of the achiral iridium catalyst ligated BIPHEP, (*R*,*R*)-**3.11** was converted to equimolar quantities of and (*R*,*R*,*S*)-**4a**, (*R*,*R*,*R*)-**4a**, respectively (Scheme 3.5).



Scheme 3.5 Catalyst directed diastereoselectivity in the transfer hydrogenative carbonyl allylation of (*R*,*R*)-**3c**.

3.2.3 Bidirectional Elongation of 1,3-Polyol

To show the utility of this approach in a related example, *O*-4-methoxybenzyl neopentyl glycol **3.12** was subjected to transfer hydrogenative carbonyl allylation employing the catalyst modified by (*R*)-Cl,MeO-BIPHEP at 120 ^{o}C. The homoallylic alcohol **3.13** was produced in 80% isolated yield and 95% enantiomeric excess. Conversion of **3.13** to the *tert*-butyldimethylsilyl ether, followed by removal of the *p*-methoxybenzyl ether delivers the primary neopentyl alcohol **3.14**. Transfer hydrogenative carbonyl allylation of **3.14** employing the catalyst modified by (*R*)-Cl,MeO-BIPHEP at 120 ^{o}C provides the homoallyl alcohol (*R*,*R*)-**3.15** in 78% isolated yield in a 12:1 diastereomeric ratio. Using the catalyst modified by (*S*)-Cl,MeO-BIPHEP at 120 ^{o}C, **3.14** is converted to the homoallyl alcohol (*S*,*R*)-**3.15** in 82% isolated yield in an 11:1 diastereomeric ratio. Using the achiral iridium catalyst modified by BIPHEP, (*R*,*R*)-**3.15** and (*S*,*R*)-**3.15** were formed in roughly equal proportion. Thus, catalyst-directed chain elongation may be conducted from either terminus of the 1,3-diol precursor with equal efficiency (Scheme 3.6).

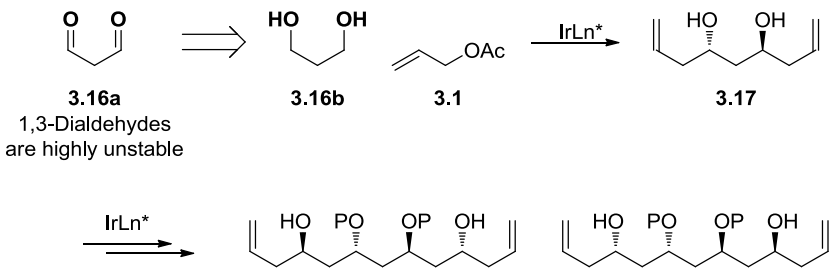


Reaction were conducted by Yu Lu.

Scheme 3.6 Bidirectional transfer hydrogenative chain elongation from both termini of neopentyl glycol.

3.3 Part Two: Elongation of 1,3-Polyol *via* Iterative Catalyst Directed Bis-allylation Reaction

1,3-Dialdehydes are very unstable compounds and cannot be utilized in one pot addition reactions. For instance, malondialdehyde can be generated through the hydrolysis of 1,1,3,3-tetramethoxypropane, capture of this dialdehyde is impeded by the fact that it is highly unstable and is generated under aqueous conditions, which promote hydration, oligomerization, and self-condensation, and preclude the use of most organometallic reagents. As we illustrated the ability to bypass stoichiometric pre-formation of aldehyde electrophiles, in carbonyl allylation from the alcohol oxidation level, potentially enables allylation processes that cannot be performed efficiently from certain unstable aldehydes. We reasoned that 1,3-propanediol could serve as a synthetic equivalent to malondialdehyde *via* successive generation and capture of mono-aldehyde intermediates (Scheme 3.7).[70]



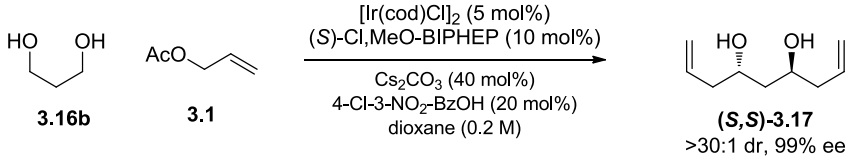
Scheme 3.7 Proposed bis-allylation reaction from alcohol oxidation level and catalyst directed diastereoselective C_2-Symmetric 1,3-polyol synthesis.

3.3.1 Reaction Optimization

Hence, the asymmetric allylation of 1,3-propanediol was explored. Using the cyclometallated catalyst generated in situ from $[Ir(cod)Cl]_2$, (*S*)-Cl,MeO-BIPHEP, 4-chloro-3-nitrobenzoic acid, and Cs_2CO_3 in dioxane solvent, the coupling of allyl acetate to propanediol at 90 ^oC for 24 h, delivers the C_2-symmetric homoallylic diol **(*S,S*)-3.17** in 56% yield, 99% ee and with better than 30:1 diastereoselectivity, as determined by chiral stationary-phase HPLC analysis.

The high levels of enantioselectivity were observed (99% ee), as the minor enantiomer of the intermediate mono adduct is converted into the meso product.[71] Moreover, increasing the reaction time to 48 h and 72 h gave 63% and 74% product, respectively. A decrease in the loading of allyl acetate from 10 to 5 equivalents diminished the isolated yield of **(*S,S*)-3.17** by only 8% (Table 3.3). This transformation was reproducible on a 20 mmol scale.

Table 3.3 Reaction optimization for bis-allylation of 1,3-propanediol.



3.16b **3.1** **(*S,S*)-3.17** >30:1 dr, 99% ee

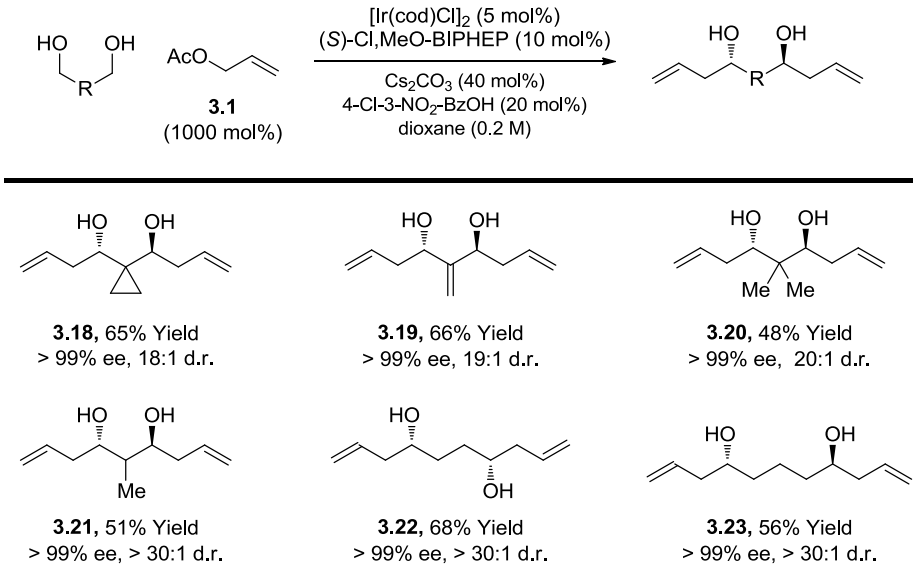
Entry[a]	**3.1** (mol%)	T (^{o}C)	Time (h)	3.17 (%)
1	1000	90	24	56
2	1000	90	48	63
3	**1000**	**90**	**72**	**74**
4	1000	90	96	66
5	500	80	72	50
6	500	90	72	43

[a] Reaction were otimized with help of Dr. In Su Kim, Yu Lu and David J. Del Valle

3.3.2 Substrate Scope

These conditions were applied to different propylene glycols. Although yields were slightly diminished in the case of 2-methyl-1,3-propanediol **3.21** and 2,2-dimethyl-1,3-propanediol (neopentyl glycol) **3.20**, uniformly high levels of enantioselectivity were observed in all cases.

Finally, the iridium-catalyzed asymmetric transfer-hydrogenative allylation of higher glycols was explored. The outcome of such transformations was uncertain, as 1,4-butanediol and 1,5-pentanediol are transformed into γ-butyrolactone and δ-valerolactone, respectively, under transfer hydrogenation conditions. Remarkably, upon exposure to conditions for iridium-catalyzed asymmetric transfer-hydrogenative allylation, 1,4-butanediol and 1,5-pentanediol are transformed into the corresponding the C_2-symmetric diols **3.22** and **3.23** in 68% and 56% yields, respectively, as single diastereo- and enantiomers (Scheme 3.8).



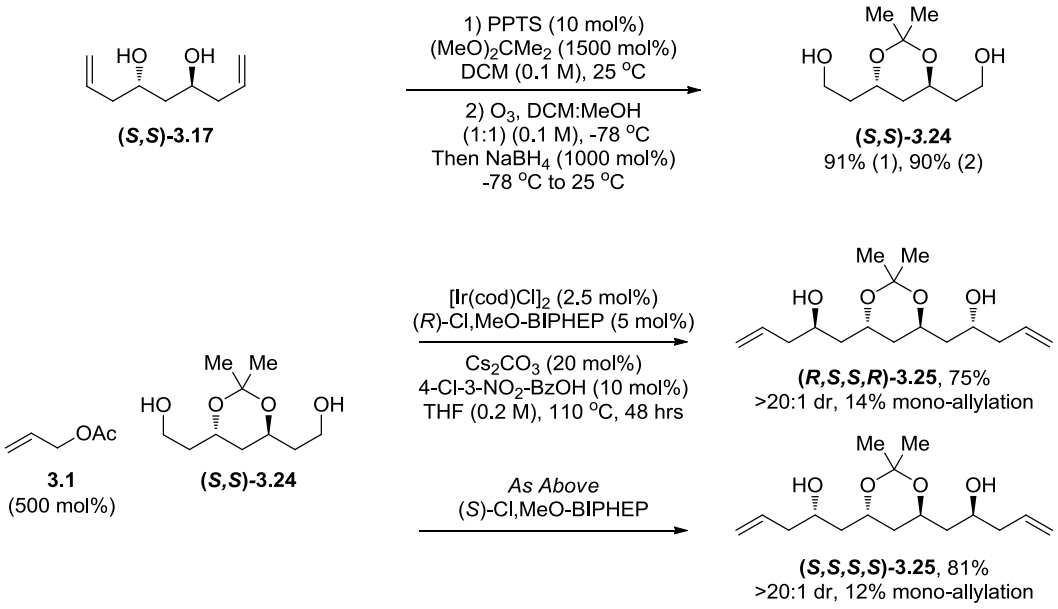
Scheme 3.8 Substrate scope for bis-allylation of terminal diols.

3.3.3 Application in C_2-Symmetric Polyol Synthesis

The step economy associated with the double allylation of propylene glycols is borne out by comparison to known methods for the synthesis of C_2-symmetric homoallylic diols. For example, in the course of a synthetic approach to (+)-phorboxazole A, the mono-TBS (*tert*-butyldimethylsilyl) derivative of C_2-symmetric diol **(*S,S*)-3.17** was prepared in 7 steps from propylene glycol **3.16b** through successive use of Brown's reagent for asymmetric carbonyl allylation, $Ipc_2(n\text{-}C_3H_5)B$.[72]

To illustrate the utility of this method in the context of two-directional chain synthesis, the C_2-symmetric diol **(*S,S*)-3.17** prepared from propylene glycol was subjected to a second round of concomitant two-directional chain elongation (Scheme 3.9). Accordingly, **(*S,S*)-3.17** was converted into the acetonide in 91% isolated yield, and was then subjected to ozonolysis. Upon complete consumption of starting material, as revealed by the persistence of a light blue color, the reaction mixture was treated with sodium borohydride to deliver the C_2-symmetric diol **(*S,S*)-3.24** in 89% isolated yield. Exposure of diol **(*S,S*)-3.24** to the iridium catalyst modified by (*R*)-Cl,MeO-BIPHEP at 110°C delivered the higher C_2-symmetric diol **(*R,S,S,R*)-3.25** in 75% isolated yield, accompanied by 14% of the orresponding monoallylation product. Using the enantiomeric catalyst modified by (*S*)-Cl,MeO-BIPHEP, **(*S,S,S,S*)-3.25** is obtained in 81%

isolated yield, accompanied by 12% of the corresponding mono-allylation product. In both cases, diastereomeric bis-adduct could not be detected by ^{1}H NMR analysis, signifying exceptional levels of catalyst-directed diastereoselectivity. The achiral iridium catalyst ligated by biphep converts **(*S,S*)-3.17** into a statistical mixture of diastereomeric adducts. The assembly of either **(*R,S,S,R*)-3.25 or (*S,S,S,S*)-3.25** in only four steps from propylene glycol illustrates the power of this new protocol for iterative two-directional chain elongation (Scheme 3.9).



Scheme 3.9 Catalyst directed bidirectional bis-allylation polyol synthesis.

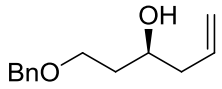
3.4 Summary

In summary, under the conditions of transfer hydrogenative carbonyl allylation, the stereochemical bias of enantiomeric iridium catalysts modified by (*R*)-or (*S*)-Cl,MeO-BIPHEP is found to override the intrinsic diastereofacial bias of transient *β*-chiral aldehyde substrates. Based on this finding, a concise iterative enantiospecific synthesis of 1,3-polyols was achieved by way of conventional (one direction) or two-directional chain extension. The step-economy associated with this approach stems from the ability to circumvent the use of chirally modified allylmetal reagents, which require multi-step preparation, and the ability to perform concomitant two-directional chain elongation directly from the alcohol oxidation level, which avoids protecting group and redox manipulations.

3.5 Experimental Section

3.5.1 Part One: Elongation of 1,3-Polyol

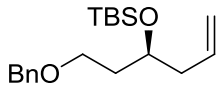
(*S*)-1-(Benzyloxy)hex-5-en-3-ol (3.5)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with 3-(benzyloxy)propanol **3.4** (3.324 g, 20.0 mmol), $[Ir(cod)Cl]_2$ (335.8 mg, 0.5 mmol), (*S*)-Cl,MeO-BIPHEP (651.5 mg, 1.0 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol) and 4-chloro-3-nitrobenzoic acid (403.1 mg, 2.0 mmol) was added THF (100 mL, 0.2 M) followed by allyl acetate (4.0 g, 40.0 mmol). The reaction mixture was allowed to stir at 120 ^oC for 20 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexanes:triethylamine, 1:15:0.01) provided **3.5** (3.625 g, 17.576 mmol) as a colorless oil in 88% yield.

TLC (SiO_2): R_f = 0.26 (ethyl acetate:hexanes, 1:15). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5H), 5.89-5.78 (m, 1H), 5.14-5.08 (m, 2H), 4.52 (s, 2H), 3.90-3.86 (m, 1H), 3.75-3.62 (m, 2H), 2.88 (br s, 1H), 2.24 (dd, *J* = 7.2, 6.0 Hz, 2H), 1.79-1.74 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 137.9, 134.8, 128.4, 127.7, 127.6, 117.6, 73.2, 70.4, 69.0, 41.9, 35.8. **HPLC:** (Chiralcel OD-H column, hexanes:*i*-PrOH = 99:1, 0.7 mL/min, 254 nm), t_{major} = 23.0 min, t_{minor} = 25.8 min; ee = 95%.

(*S*)-(1-(Benzyloxy)hex-5-en-3-yloxy)(tert-butyl)dimethylsilane (3.6)

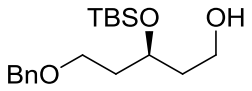


To a solution of **3.5** (2.98 g, 14.446 mmol) in DMF (14.5 mL, 1.0 M) was added imidazole (2.46 g, 36.116 mmol) and TBSCl (4.35 g, 28.892 mmol) at room temperature. The reaction mixture was allowed to stir overnight at 50 ^oC, at which point H_2O (30 mL) was added. The reaction mixture was extracted with ether (60 mL x 3) and the combined organic extracts were dried

(Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by column chromatography (SiO2: ethyl acetate:hexanes, 1:49) provided **3.6** (4.15 g, 12.947 mmol) as a colorless oil in 90% yield.

TLC (SiO_2): R_f = 0.60 (ethyl acetate:hexanes, 1:19). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 5.86-5.76 (m, 1H), 5.06-5.00 (m, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H) 3.93-3.87 (m, 1H), 3.57-3.52 (m, 2H), 2.29-2.17 (m, 2H), 1.84-1.66 (m, 2H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.5, 134.9, 128.3, 127.6, 127.5, 117.0, 72.9, 68.9, 67.0, 42.3, 36.7, 25.8, 18.0, -4.4, -4.7.

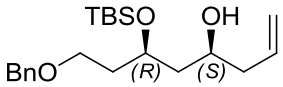
(*S*)-5-(Benzyloxy)-3-(tert-butyldimethylsilyloxy)pentan-1-ol (3.7)



To a solution of **3.6** (3.55 g, 11.075 mmol) in methanol (74 mL, 0.15 M) was added 3-5 drops of solution of Sudan III (1.5 nM in methanol) to make the solution pink-light pink. O_3 (2.0 $Lmin^{-1}$, 15 V) was bubbled through the solution for 40 min (till the solution become colorless) at -78 ^oC. The reaction mixture was sparged with argon for 10 min at -78 ^oC to remove residual O_3, at which point $NaBH_4$ (4.2 g, 110.75 mmol) was added. The reaction mixture was allowed to reach room temperature over 2 hr. H_2O (20 mL) was added and the reaction mixture was concentrated to ~25 mL in vacuo. H_2O (50 mL) was added and the aqueous phase was extracted with ethyl acetate (100 mL x 3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by column chromatography (SiO2: ethyl acetate:hexanes, 1:6) provided **3.7** (3.30 g, 10.168 mmol) as a colorless oil in 92% yield.

TLC (SiO_2): R_f = 0.22 (ethyl acetate:hexanes, 1:4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.01 (m, 1H), 3.80 (m, 1H), 3.70 (m, 1H), 3.52 (t, *J* = 6.3 Hz, 2H), 2.53 (br s, 1H), 1.91-1.78 (m, 3H), 1.70-1.62 (m, 1H) 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.3, 128.3, 127.6, 127.5, 73.0, 68.9, 66.7, 59.9, 38.3, 36.7, 25.8, 17.9, -4.7.

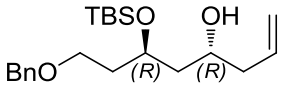
(4*S*,6*R*)-8-(Benzyloxy)-6-(tert-butyldimethylsilyloxy)oct-1-en-4-ol ((*R*,*S*)-3.8)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with **3.7** (649.0 mg, 2.0 mmol), $[Ir(cod)Cl]_2$ (34.0 mg, 0.05 mmol), (*S*)-Cl,MeO-BIPHEP (65.1 mg, 0.1 mmol), Cs_2CO_3 (130.0 mg, 0.4 mmol) and 4-chloro-3-nitrobenzoic acid (40.0 mg, 0.2 mmol) was added THF (10 mL, 0.2 M) followed by allyl acetate (400.0 mg, 4.0 mmol). The reaction mixture was allowed to stir at 100 ^oC for 40 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexanes:triethylamine, 1:9:0.01) provided **(*R*,*S*)-3.8** (576.0 mg, 1.58 mmol) as a colorless oil in 79% yield.

TLC (SiO_2): R_f = 0.41 (ethyl acetate:hexanes, 1:4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 5.87-5.76 (m, 1H), 5.13-5.07 (m, 2H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.11-4.05 (m, 1H), 3.84-3.77 (m, 1H), 3.52 (t, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 1.6 Hz, 1H), 2.23-2.19 (m, 2H), 1.91-1.77 (m, 2H), 1.69-1.64 (m, 1H), 1.60-1.52 (m, 1H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.3, 134.8, 128.3, 127.6, 127.5, 117.5, 73.0, 70.1, 69.6, 66.5, 42.8, 42.6, 25.8, 17.8, -4.3, -4.68. **FTIR** (neat): υ 3448, 3067, 2949, 2928, 2856, 2360, 1641, 1496, 1472, 1454, 1409, 1360, 1253, 1076, 1028, 1003, 912, 835, 774, 734, 697, 667 cm^{-1}. **HRMS** (CI) Calcd. for $C_{21}H_{37}O_3Si$ (M+1): 365.2512, Found: 365.2519.

(4*R*,6*R*)-8-(Benzyloxy)-6-(tert-butyldimethylsilyloxy)oct-1-en-4-ol ((*R*,*R*)-3.8)

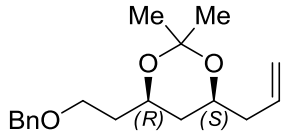


To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with **3.7** (649.0 mg, 2.0 mmol), $[Ir(cod)Cl]_2$ (34.0 mg, 0.05 mmol), (*R*)-Cl,MeO-BIPHEP (65.1 mg, 0.1 mmol), Cs_2CO_3 (130.0 mg, 0.4 mmol) and 4-chloro-3-nitrobenzoic acid (40.0 mg, 0.2 mmol) was added THF (10 mL, 0.2 M) followed by allyl acetate (400.0 mg, 4.0 mmol). The reaction mixture was allowed to stir at 100 ^oC for 40 hr, at which point the reaction mixture was evaporated onto silica

gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexanes:triethylamine, 1:9:0.01) provided **(*R*,*R*)-3.8** (516.0 mg, 1.42 mmol) as a colorless oil in 71% yield.

TLC (SiO_2): R_f = 0.39 (ethyl acetate:hexanes, 1:4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 5.85-5.75 (m, 1H), 5.15-5.05 (m, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.22-4.17 (m, 1H), 4.02-3.95 (m, 1H), 3.54-3.46 (m, 2H), 3.36 (d, *J* = 2.0 Hz, 1H), 2.26-2.12 (m, 2H), 1.98-1.80 (m, 2H), 1.69-1.55 (m, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.3, 134.8, 128.4, 127.6, 127.6, 117.5, 73.0, 70.2, 69.7, 66.5, 42.7, 42.2, 37.7, 25.8, 17.9, -4.3, -4.6. **FTIR** (neat): υ 3457, 3071, 3021, 2949, 2928, 2889, 2856, 1641, 1495, 1471, 1454, 1361, 1254, 1071, 1027, 1002, 911, 835, 733, 697, 665 cm^{-1}. **HRMS** (CI) Calcd. for $C_{21}H_{37}O_3Si$ (M+1): 365.2512, Found: 365.2511.

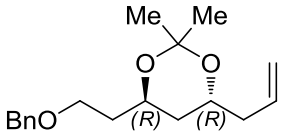
(4*S*,6*R*)-4-Allyl-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane ((*R*,*S*)-3.9)



To a solution of **((*R*,*S*)-3.8** (554.0 mg, 1.519 mmol) in methanol (15mL, 0.1 M) was added *p*-toluenesulfonic acid monohydrate (29.0 mg, 0.152 mmol). The reaction mixture was stirred for 1 h at room temperature. TLC analysis showed complete consumption of the starting material. The reaction mixture was diluted with 2,2-dimethoxypropane (12.60 g, 15 mL, 120.979 mmol) and was stirred for 1 hr at room temperature. After concentrated in vacuo, the residue was diluted with 2,2-dimethoxypropane (6.30 g, 7.5 mL, 60.489 mmol) and was again concentrated in vacuo. 2,2-Dimethoxypropane (12.60 g, 15 mL, 120.979 mmol) was added and the reaction mixture was stirred for 15 min. The reaction mixture was diluted with dichloromethane (200 mL) and washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexanes:triethylamine, 1:9:0.01) provided **(*R*,*S*)-3.9** (370.0 mg, 1.274 mmol) as a colorless oil in 84% yield.

TLC (SiO_2): R_f = 0.49 (ethyl acetate:hexanes, 1:4). **^{1}H NMR**[3] (400 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 5.85-5.74 (m, 1H), 5.11-5.03 (m, 2H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.06-4.00 (m, 1H), 3.91-3.84 (m, 1H), 3.62-3.50 (m, 2H), 2.34-2.27 (m, 1H), 2.18-2.10 (m, 1H), 1.82-1.68 (m, 2H), 1.50 (dt, *J* = 13.2, 2.4 Hz, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.15 (dd, *J* = 13.2, 11.6 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.5, 134.2, 128.4, 127.6, 127.6, 117.1, 98.5, 73.0, 68.6, 66.2, 66.0, 40.8, 36.6, 36.5, 30.2, 19.9. **FTIR** (neat): υ 3071, 3025, 2991, 2942, 2860, 1723, 1642, 1496, 1454, 1379, 1264, 1198, 1170, 1146, 1027, 997, 963, 913, 873, 801, 734, 697 cm^{-1}. **HRMS** (CI) Calcd. for $C_{18}H_{27}O_3$ (M+1): 291.1960, Found: 291.1954.

(4*R*,6*R*)-4-Allyl-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane ((*R*,*R*)-3.9)

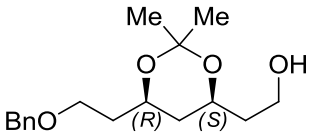


To a solution of **(*R*,*R*)-3.8** (497.0 mg, 1.363 mmol) in methanol (14mL, 0.1 M) was added *p*-toluenesulfonic acid monohydrate (26.0 mg, 0.136 mmol). The reaction mixture was stirred for 1 h at room temperature, at which point TLC analysis revealed complete consumption of the starting material. The reaction mixture was diluted with 2,2-dimethoxypropane (11.80 g, 14 mL, 113.298 mmol) and stirred for 1 h at room temperature. After concentrated in vacuo, the residue was diluted with 2,2-dimethoxypropane (6.88 g, 7 mL, 56.457 mmol) and was again concentrated in vacuo. 2,2-Dimethoxypropane (11.80 g, 14 mL, 113.298 mmol) was added and the reaction mixture was stirred for 15 min. The reaction mixture was diluted with dichloromethane (200 mL) and washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes:triethylamine, 1:9:0.01) provided **(*R*,*R*)-3.9** (341.0 mg, 1.174 mmol) as a colorless oil in 84% yield.

TLC (SiO_2): R_f = 0.48 (ethyl acetate:hexanes, 1:4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 5.84-5.74 (m, 1H), 5.12-5.02 (m, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.03-3.96 (m, 1H), 3.89-3.82 (m, 1H), 3.59-3.50 (m, 2H), 2.34-2.27 (m, 1H), 2.22-2.15 (m, 1H), 1.80-1.74 (m, 2H), 1.66-1.55 (m, 2H), 1.34 (s, 3H), 1.33 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.5, 134.5, 128.4, 127.7, 127.6, 116.8, 100.3, 73.1, 66.6, 66.2, 63.7, 40.2, 38.0, 36.0,

24.8. **FTIR** (neat): υ 3067, 3029, 2985, 2938, 2856, 1642, 1496, 1454, 1378, 1222, 1098, 1028, 992, 912, 802, 735, 697 cm^{-1}. **HRMS** (CI) Calcd. for $C_{18}H_{27}O_3$ (M+1): 291.1960, Found: 291.1967.

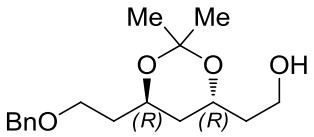
2-((4*S*,6*R*)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol ((*R*,*S*)-3.10)



To a solution of **(*R*,*S*)-3.9** (310.0 mg, 1.068 mmol) in methanol:dichloromethane (7:3 v/v, 11 mL, 0.1 M) was added 3-5 drops of solution of Sudan III (1.5 nM in methanol) to make the solution pink-light pink. O_3 (2.0 $Lmin^{-1}$, 15 V) was bubble through the solution for 12 min (till the solution become colorless) at -78 ^oC. The reaction mixture was sparged with argon for 10 min at -78 ^oC to remove residual O_3, at which point $NaBH_4$ (404.0 mg, 10.675 mmol) was added. The reaction mixture was allowed to reach room temperature over 2 hr. H_2O (5 mL) was added and the reaction mixture was concentrated to ~5 mL in vacuo. H_2O (10 mL) was added and the aqueous phase was extracted with ethyl acetate (30 mL x 3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by column chromatography (SiO2: ethyl acetate:hexanes:triethylamine, 1:1:0.01) provided **(*R*,*S*)-3.10** (281.0 mg, 0.954 mmol) as a colorless oil in 89% yield.

TLC (SiO_2): R_f = 0.22 (ethyl acetate:hexanes, 1:1.5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.14-4.04 (m, 2H), 3.81-3.72 (m, 2H), 3.62-3.50 (m, 2H), 2.57 (t, *J* = 4.8 Hz, 1H), 1.81-1.67 (m, 4H), 1.48-1.24 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.5, 128.4, 127.6, 98.7, 73.0, 69.5, 66.1, 66.0, 61.0, 38.0, 36.8, 36.5, 30.2, 20.0. **FTIR** (neat): υ 3437, 3088, 3063, 3029, 2991, 2942, 2864, 1496, 1454, 1380, 1264, 1198, 1165, 1106, 1053, 1227, 957 cm^{-1}. **HRMS** (CI) Calcd. for $C_{17}H_{27}O_4$ (M+1): 295.1909, Found: 295.1916.

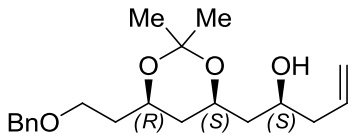
2-((4*R*,6*R*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol ((*R*,*R*)-3.10)



To a solution of **(*R*,*R*)-3.9** (312.0 mg, 1.074 mmol) in methanol:dichloromethane (7:3 v/v, 11 mL, 0.1 M) was added 3-5 drops of solution of Sudan III (1.5 nM in methanol) to make the solution pink-light pink. O_3 (2.0 $Lmin^{-1}$, 15 V) was bubbled through the solution for 10 min (till the solution become colorless) at -78 ^oC. The reaction mixture was sparged with argon for 10 min at -78 ^oC to remove residual O_3, at which point $NaBH_4$ (407.0 mg, 10.744 mmol) was added. The reaction mixture was allowed to reach room temperature over 2 hr. H_2O (5 mL) was added and the solution was concentrated to ~5 mL in vacuo. H_2O (10 mL) was added and the aqueous phase was extracted with ethyl acetate (30 mL x 3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by column chromatography (SiO2: ethyl acetate:hexanes:triethylamine, 1:1:0.01) provided **(*R*,*R*)-3.10** (289.0 mg, 0.982 mmol) as a colorless oil in 91% yield.

TLC (SiO_2): R_f = 0.22 (ethyl acetate:hexanes, 1:1.5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.08-3.98 (m, 2H), 3.81-3.71 (m, 2H), 3.60-3.51 (m, 2H), 2.58 (br s, 1H), 1.82-1.72 (m, 4H), 1.71-1.60 (m, 2H), 1.37 (s, 3H), 1.33 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.4, 128.4, 127.7, 127.6, 100.5, 73.1, 67.0, 66.5, 63.7, 61.2, 38.3, 37.6, 35.9, 24.8, 24.7. **FTIR** (neat): υ 3451, 3084, 3063, 3025, 3985, 3938, 3862, 1496, 1454, 1379, 1124, 1096, 1053, 1027, 979, 902, 880, 794, 736, 697 cm^{-1}. **HRMS** (CI) Calcd. for $C_{17}H_{27}O_4$ (M+1): 295.1909, Found: 295.1915.

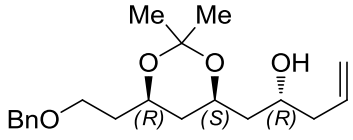
(*S*)-1-((4*S*,6*R*)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)pent-4-en-2-ol ((*R*,*S*,*S*)-3.11)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with **(*R*,*S*)-3.10** (59.0 mg, 0.2 mmol), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol), (*S*)-Cl,MeO-BIPHEP (6.5 mg, 0.01 mmol), Cs_2CO_3 (13.0 mg, 0.04 mmol) and 4-chloro-3-nitrobenzoic acid (4.0 mg, 0.02 mmol) was added THF (1.0 mL, 0.2 M) followed by allyl acetate (40 mg, 0.4 mmol). The reaction mixture was allowed to stir at 100 ^{o}C for 40 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexanes:triethylamine, 1:3:0.01) provided **(*R*,*S*,*S*)-3.11** (55.5 mg, 0.166 mmol) as a colorless oil in 83% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 5.89-5.78 (m, 1H), 5.13-5.06 (m, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.14-4.03 (m, 2H), 3.90-3.84 (m, 1H), 3.61-3.49 (m, 3H), 2.29-2.15 (m, 2H), 1.81-1.68 (m, 2H), 1.60-1.56 (m, 2H), 1.50-1.19 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.4, 134.8, 128.4, 127.7, 127.6, 117.4, 98.7, 73.0, 71.0, 70.3, 66.0, 65.9, 42.2, 42.0, 36.4, 30.2, 20.0. **FTIR** (neat): υ 3507, 3029, 2991, 2941, 2863, 1720, 1641, 1496, 1453, 1432, 1380, 1314, 1269, 1199, 1166, 1027, 996, 957, 914, 874, 794, 714, 698 cm^{-1}. **HRMS** (CI) Calcd. for $C_{20}H_{31}O_4$ (M+1): 335.2222, Found: 335.2230.

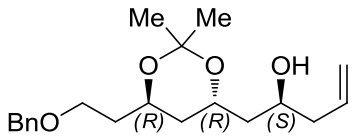
(*R*)-1-((4*S*,6*R*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)pent-4-en-2-ol ((*R*,*S*,*R*)-3.11)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with **(*R*,*S*)-3.10** (59.0 mg, 0.2 mmol), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol), (*R*)-Cl,MeO-BIPHEP (6.5 mg, 0.01 mmol), Cs_2CO_3 (13.0 mg, 0.04 mmol) and 4-chloro-3-nitrobenzoic acid (4.0 mg, 0.02 mmol) was added THF (1.0 mL, 0.2 M) followed by allyl acetate (40 mg, 0.4 mmol). The reaction mixture was allowed to stir at 100 ^oC for 40 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexanes:triethylamine, 1:3:0.01) provided **(*R*,*S*,*R*)-3.11** (60.9 mg, 0.182 mmol) as a colorless oil in 91% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 5.88-5.78 (m, 1H), 5.14-5.09 (m, 2H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.22-4.16 (m, 1H), 4.10-4.03 (m, 1H), 3.97-3.90 (m, 1H), 3.62-3.50 (m, 2H), 2.83 (d, *J* = 4.0 Hz, 1H), 2.23 (t, *J* = 7.2 Hz, 2H), 1.82-1.68 (m, 2H), 1.62 (t, *J* = 5.6 Hz, 2H), 1.46-1.26 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.5, 135.0, 128.4, 127.7, 127.6, 117.6, 98.7, 73.0, 67.5, 67.1, 66.1, 42.0, 41.6, 36.52, 36.50, 30.2, 19.7. **FTIR** (neat): υ 3459, 3071, 3029, 2992, 2941, 1721, 1641, 1496, 1453, 1432, 1380, 1266, 1165, 1198, 1146, 1099, 1027, 997, 958, 913, 874, 713, 698 cm^{-1}. **HRMS** (CI) Calcd. for $C_{20}H_{31}O_4$ (M+1): 335.2222, Found: 335.2231.

(*S*)-1-((4*R*,6*R*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)pent-4-en-2-ol ((*R*,*R*,*S*)-3.11)

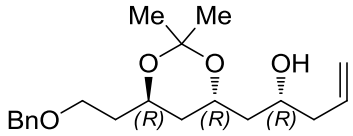


To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with **(*R*,*R*)-3.10** (59.0 mg, 0.2 mmol), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol), (*S*)-Cl,MeO-BIPHEP (6.5 mg, 0.01 mmol), Cs_2CO_3 (13.0 mg, 0.04 mmol) and 4-chloro-3-nitrobenzoic acid (4.0 mg, 0.02 mmol) was added THF (1.0 mL, 0.2 M) followed by allyl acetate (40 mg, 0.4 mmol). The reaction mixture was allowed to stir at 100 ^oC for 40 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl

acetate:hexanes:triethylamine, 1:3:0.01) provided **(*R*,*R*,*S*)-3.11** (50.0 mg, 0.149 mmol) as a colorless oil in 74% yield.

TLC (SiO_2): R_f = 0.24 (ethyl acetate:hexanes, 1:2.3). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 5.88-5.78 (m, 1H), 5.14-5.09 (m, 2H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.19-4.12 (m, 1H), 4.05-3.97 (m, 1H), 3.94-3.87 (m, 1H), 3.59-3.50 (m, 2H), 2.64 (d, *J* = 4.1 Hz, 1H), 2.28-2.19 (m, 2H), 1.81-1.75 (m, 2H), 1.72-1.55 (m, 4H), 1.36 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.4, 134.9, 128.4, 127.7, 127.5, 117.7, 100.5, 73.1, 67.7, 66.5, 64.3, 63.8, 41.9, 41.1, 38.0, 35.9, 24.7, 24.6. **FTIR** (neat): υ 3456, 3067, 3029, 2985, 2938, 1721, 1641, 1496, 1254, 1380, 1274, 1223, 1098, 1027, 996, 910, 841, 800, 713, 698 cm^{-1}. **HRMS** (CI) Calcd. for $C_{20}H_{31}O_4$ (M+1): 335.2222, Found: 335.2226.

(*R*)-1-((4*R*,6*R*)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)pent-4-en-2-ol ((*R*,*R*,*R*)-3.11)

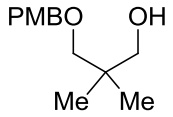


To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with **(*R*,*R*)-3.10** (59.0 mg, 0.2 mmol), $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol), (*S*)-Cl,MeO-BIPHEP (6.5 mg, 0.01 mmol), Cs_2CO_3 (13.0 mg, 0.04 mmol) and 4-chloro-3-nitrobenzoic acid (4.0 mg, 0.02 mmol) was added THF (1.0 mL, 0.2 M) followed by allyl acetate (40 mg, 0.4 mmol). The reaction mixture was allowed to stir at 100 ^oC for 40 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexanes:triethylamine, 1:3:0.01) provided **(*R*,*R*,*R*)-3.11** (57.2 mg, 0.171 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.33 (ethyl acetate:hexanes, 1:2.3). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 5.88-5.78 (m, 1H), 5.12-5.07 (m, 2H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.09-3.98 (m, 2H), 3.86-3.80 (m, 1H), 3.58-3.49 (m, 3H), 2.29-2.15 (m, 2H), 1.79-1.74 (m, 2H), 1.69-1.54 (m, 4H), 1.38 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.3, 134.8, 128.3, 127.6, 127.5, 117.3, 100.6, 73.1, 71.2, 67.9, 66.4, 63.5, 41.9, 41.6, 38.6, 35.8, 24.8, 24.6.

FTIR (neat): υ 3639, 3507, 3025, 2985, 2937, 2857, 2358, 1721, 1641, 1496, 1454, 1380, 1313, 1274, 1223, 1168, 1095, 1027, 994, 908, 796, 697 cm^{-1}. **HRMS** (CI) Calcd. for $C_{20}H_{31}O_4$ (M+1): 335.2222, Found: 335.2228.

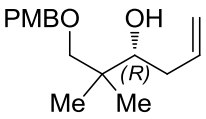
3-(4-Methoxybenzyloxy)-2,2-dimethylpropan-1-ol (3.12)



To a solution of 2,2-dimethylpropane-l,3-diol (2.08 g, 20.0 mmol) in DMF (20 mL, 1.0 M) was added sodium hydride (60% w/w in mineral oil, 0.96 g, 24.0 mmol) in portions at 0 °C. The reaction mixture was allowed to stir for 30 min at 0 °C, at which point 4-methoxybenzyl chloride (3.13 g, 20.0 mmol) and TBAI (0.74 g, 2.0 mmol) were added. The reaction mixture was allowed to reach room temperature over 2 hr and was then allowed to stir overnight. Saturated aqueous NH_4Cl solution (50 mL) was added and the reaction mixture was extracted with diethyl ether (60 mL x 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexane, 1:6 to 1:2) provided **3.12** (3.78 g, 16.90 mmol) as a colorless oil in 84% yield.

TLC (SiO_2): R_f = 0.46 (ethyl acetate:hexane, 1:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.44 (s, 2H), 3.81 (s, 3H), 3.44 (s, 2H), 3.29 (s, 2H), 2.48 (br s, 1H), 0.92 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.4, 130.6, 129.3, 114.0, 78.7, 73.3, 71.3, 55.4, 36.5, 22.1.

(R)-1-(4-Methoxybenzyloxy)-2,2-dimethylhex-5-en-3-ol (3.13)

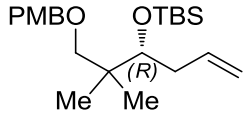


To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol), (*R*)-Cl,MeO-BIPHEP (6.9 mg, 0.01 mmol), Cs_2CO_3 (13.1 mg, 0.04 mmol) and 4-chloro-3-nitrobenzoic acid (4.1 mg, 0.02 mmol) was added THF (1.0 mL, 0.2 M)

followed by allyl acetate (40 mg, 0.4 mmol). The reaction mixture was allowed to stir at 90 °C for 0.5 hr and was cooled to room temperature. **3.12** (44.9 mg, 0.2 mmol) was added to the reaction mixture and the reaction was allowed to stir at 120 °C for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexane, 1:20 to 1:8) provided **3.13** (42.3 mg, 0.16 mmol) as a colorless oil in 80% yield.

TLC (SiO_2): R_f = 0.48 (ethyl acetate:hexane, 1:4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.97-5.87 (m, 1H), 5.12-5.06 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.51 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.35 (d, *J* = 8.8 Hz, 1H), 3.26 (d, *J* = 8.8 Hz, 1H), 2.96 (br s, 1H), 2.29-2.24 (m, 1H), 2.09-2.01 (m, 1H), 0.92 (s, 3H), 0.90 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.4, 137.1, 130.2, 129.4, 116.8, 114.0, 79.5, 77.8, 73.4, 55.5, 38.5, 36.8, 22.9, 19.9. **HPLC**: (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 254 nm), t_{major} = 18.3 min, t_{minor} = 16.5 min; *ee* = 95%.

(*R*)-(1-(4-Methoxybenzyloxy)-2,2-dimethylhex-5-en-3-yloxy)(*tert*-butyl)dimethylsilane (3.13a)

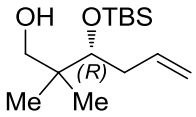


To a solution of **3.13** (0.68 g, 2.580 mmol) in dichloromethane (26 mL, 0.1 M) was added 2,6-lutidine (1.10 g, 10.320 mmol) and TBSOTf (1.36 g, 5.160 mmol) was added dropwise at -78 ^oC. The resulting solution was stirred for 1 hr at -78 °C. The reaction mixture was quenched with saturated NH_4C1 solution (60 mL and was extracted with dichloromethane (60 mL x 3). The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexane, 1:20) provided **3.13a** (0.90 g, 2.38 mmol) as a colorless oil in 92% yield.

TLC (SiO_2): R_f = 0.50 (ethyl acetate:hexane, 1:15). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.93-5.83 (m, 1H), 5.02-4.95 (m, 2H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 3.81 (s, 3H), 3.70-3.67 (dd, *J* = 6.0, 4.8 Hz, 1H), 3.23 (d, *J* =

8.4 Hz, 1H), 3.11 (d, *J* = 8.4 Hz, 1H), 2.39-2.32 (m, 1H), 2.18-2.11 (m, 1H), 0.90 (s, 3H), 0.89 (s, 9H), 0.87 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.2, 137.8, 131.3, 129.2, 115.8, 113.9, 76.0, 73.0, 55.5, 40.5, 38.2, 26.4, 21.9, 21.4, 18.5, -3.1, -4.2. **FTIR (neat)**: υ 3072, 2955, 2927, 2895, 2851, 1610, 1518, 1249, 1078, 1033, 903, 834, 770, 660 cm^{-1}. **HRMS** (ESI) Calcd. for $C_{22}H_{38}NaO_3Si$ $[M+Na]^+$: 401.2485, Found: 401.2482.

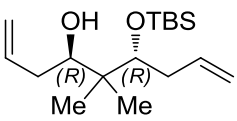
(*R*)-3-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylhex-5-en-l-ol (3.14)



To a solution of compound **3.13a** (866 mg, 2.29 mmol) in dichloromethane:*p*H 7 buffer (10:1 v/v, 22 mL) was added DDQ (642 mg, 2.74 mmol) in portions at 0 °C. The reaction mixture was stirred for 2 hr at 0 °C and quenched with H_2O (20 mL). The aqueous layer was extracted with dichloromethane (30 mL x 3). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexanes 1:20) provided **3.14** (500.0 mg, 1.934 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.47 (ethyl acetate:hexanes, 1:6). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.94-5.83 (m, 1H), 5.08-5.00 (m, 1H), 3.72 (d, *J* = 10.8 Hz, 1H), 3.60 (t, *J* = 5.6 Hz, 1H), 3.25 (d, *J* = 10.8 Hz, 1H), 2.77 (s, 1H), 2.50-2.42 (m, 1H), 2.30-2.23 (m, 1H), 1.12 (s, 3H), 0.89 (s, 9H), 0.79 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 136.7, 116.7, 80.1, 70.4, 39.9, 38.4, 26.2, 23.9, 22.0, 18.3, -3.4, -4.2. **FTIR** (neat): υ 3430, 3075, 2955, 2923, 2885, 2854, 1473, 1249, 1090, 1043, 1002, 910, 834, 770, 660 cm^{-1}. **HRMS** (ESI) Calcd. for $C_{14}H_{30}O_2SiNa$ $[M+Na]^+$: 281.1907, Found: 281.1907.

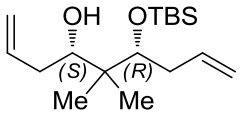
(4*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-5,5-dimethylnona-l,8-dien-4-ol ((*R*,*R*)-3.15)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol), (*R*)-Cl,MeO-BIPHEP (6.9 mg, 0.01 mmol), Cs_2CO_3 (13.1 mg, 0.04 mmol) and 4-chloro-3-nitrobenzoic acid (4.1 mg, 0.02 mmol) was added THF (1.0 mL, 0.2 M) followed by allyl acetate (40 mg, 0.4 mmol). The reaction mixture was allowed to stir for 0.5 hr at 90 °C and was cooled to room temperature. **3.14** (51.7 mg, 0.2 mmol) was added and the reaction mixture was allowed to stir for 48 hr at 120 °C, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexane, 1:40) provided **(*R*,*R*)-15** (46.7 mg, 0.156 mmol) as a colorless oil in 78% yield.

TLC (SiO_2): R_f = 0.38 (ethyl acetate:hexane, 1:20). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.00-5.83 (m, 2H), 5.15-5.02 (m, 4H), 4.19 (s, 1H), 3.88-3.85 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.58-3.55 (dd, *J* = 6.4, 4.4 Hz, 1H), 2.56-2.49 (m, 1H), 2.37-2.30 (m, 1H), 2.15-2.12 (m, 2H), 1.00 (s, 3H), 0.90 (s, 9H), 0.80 (s, 3H), 0.10 (s,3H), 0.09 (s,3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 142.5, 142.1, 122.4, 121.9, 88.8, 80.7, 46.8, 43.3, 42.1, 31.7, 28.9, 26.1, 23.7, 1.9, 1.4.

(4*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-5,5-dimethylnona-l,8-dien-4-ol ((*S*,*R*)-3.15)



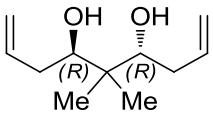
To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol), (*S*)-Cl,MeO-BIPHEP (6.9 mg, 0.01 mmol), Cs_2CO_3 (13.1 mg, 0.04 mmol) and 4-chloro-3-nitrobenzoic acid (4.1 mg, 0.02 mmol) was added THF (1.0 mL, 0.2 M) followed by allyl acetate (40 mg, 0.4 mmol). The reaction mixture was allowed to stir for 0.5 hr at 90 °C and was cooled to room temperature. **3.14** (51.7 mg, 0.2 mmol) was added and the reaction mixture was allowed to stir for 48 hr at 120 °C, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexane, 1:40) provided **(*S*,*R*)-3.15** (48.9 mg, 0.164 mmol) as a colorless oil in 82% yield.

TLC (SiO_2): R_f = 0.34 (ethyl acetate:hexane, 1:20). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.96-5.80 (m, 2H), 5.16-4.98 (m, 4H), 3.72-3.70 (t, *J* = 5.2 Hz, 1H), 3.58-3.54 (dt, *J* = 10.4, 2.4 Hz, 1H), 2.52-2.45 (m, 1H), 2.40-2.35 (m, 1H), 2.25-2.18 (m, 1H), 2.04-2.00 (m, 1H), 1.91 (d, *J* = 3.6 Hz,

1H), 0.92 (s, 3H), 0.90 (s, 9H), 0.82 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 137.7, 136.7, 118.0, 116.1, 78.0, 74.9, 43.0, 38.4, 37.0, 26.3, 19.7, 19.4, 18.5, -3.0, -4.1. **FTIR** (neat): υ 3497, 3079, 2958, 2930, 2885, 2857, 1723, 1255, 1090, 1055, 1002, 910, 834, 774, 672 cm^{-1}. **HRMS** (ESI) Calcd. for $C_{17}H_{34}NaO_2Si$ $[M+Na]^+$: 321.2226, Found: 321.2224.

3.5.2 Part Two: Elongation *via* Bis-allylation Reaction

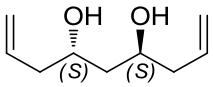
(4*R*,6*R*)-5,5-Dimethylnona-l,8-diene-4,6-diol ((*R*,*R*)-3.17)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (6.8 mg, 0.01 mmol), (*R*)-Cl,MeO-BIPHEP (13.6 mg, 0.02 mmol), Cs_2CO_3 (26.2 mg, 0.08 mmol) and 4-chloro-3-nitrobenzoic acid (8.2 mg, 0.04 mmol) was added THF (1.0 mL, 0.2 M) followed by allyl acetate (100 mg, 1.0 mmol). The reaction mixture was allowed to stir for 0.5 hr at 90 °C and was cooled to room temperature. **3.16b** (20.8 mg, 0.2 mmol) was added and the reaction mixture was allowed to stir for 4 days at 110 °C, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexane, 1:10 to 1:4) provided **(*R*,*R*)-3.17** (17.0 mg, 0.092 mmol) as a colorless oil in 46% yield.

TLC (SiO_2): R_f = 0.34 (ethyl acetate:hexane, 1:4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.94-5.83 (m, 2H), 5.18-5.13 (m, 4H), 3.58-3.55 (dd, *J* = 10.4, 2.0 Hz, 2H), 2.97 (s, 2H), 2.35-2.30 (m, 2H), 2.19-2.07 (m, 2H), 0.93 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 136.2, 117.8, 77.4, 40.0, 36.5, 20.9. **HPLC**: Enantiomeric excess was determined by HPLC analysis of the mono 4-nitrobenzoate derivative of the product. (Chiralcel AD-H column, hexanes:*i*-PrOH = 90:10, 0.5 mL/min, 254 nm), t_{major}= 19.4 min, t_{minor} = 17.2 min; *ee* = 98%

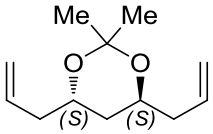
(4*S*,6*S*)-Nona-l,8-diene-4,6-diol ((*S*,*S*)-3.17)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (13.6 mg, 0.02 mmol), (*S*)-Cl,MeO-BIPHEP (27.4 mg, 0.04 mmol), Cs_2CO_3 (52.4 mg, 0.16 mmol) and 4-chloro-3-nitrobenzoic acid (16.2 mg, 0.08 mmol) was added THF (1.0 mL, 0.2 M) followed by allyl acetate (200 mg, 2.0 mmol). The reaction mixture was allowed to stir for 0.5 hr at 90 °C and was cooled to room temperature. **3.16b** (30.5 mg, 0.2 mmol) was added and the reaction mixture was allowed to stir for 48 hr at 110 °C, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexane, 1:4 to 1:1) provided **(*S*,*S*)-3.17** (43.4 mg, 0.28 mmol) as a colorless oil in 70% yield.

TLC (SiO_2): R_f = 0.44 (ethyl acetate:hexane, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.86-5.77 (m, 2H), 5.16-5.10 (m, 4H), 4.02-3.96 (m, 2H), 2.59 (s, 2H), 2.28-2.24 (m, 4H), 1.64-1.62 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.6, 118.1, 68.1, 42.0, 41.5. **HPLC**: Enantiomeric excess was determined by HPLC analysis of the mono 4-nitrobenzoate derivative of the product. (Chiralcel OJ-H column, hexanes:*i*-PrOH = 92:8, 0.8 mL/min, 254 nm), t_{major} = 12.5 min, t_{minor} =21.9 min; *ee* > 99%.

(4*S*,6*S*)-4,6-Diallyl-2,2-dimethyl-l,3-dioxane ((*S*,*S*)-3.24a)

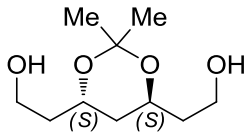


To a solution of **(*S*,*S*)-3.17** (52.2 mg, 0.334 mmol) in dichloromethane (3.4 mL, 0.1 M) was added 2,2-dimethoxypropane (0.64 mL, 5.01 mmol) and PPTS (8.6 mg, 0.034 mmol) at room temperature. The reaction mixture was stirred for 30 min, at which point saturated $NaHCO_3$ (10 mL) was added and the reaction mixture was extracted with dichloromethane (15 mL x 3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of

the residue by column chromatography (SiO_2: ethyl acetate:hexane, 1:20 to 1:15, with 0.1% TEA) provided **(*S*,*S*)-3.24a** (59.6 mg, 0.304 mmol) as a colorless oil in 91% yield.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexane, 20:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.85-5.74 (m, 2H), 5.12-5.03 (m, 4H), 3.89-3.82 (m, 2H), 2.34-2.26 (m, 1H), 2.23-2.15 (m, 1H), 1.63-1.59 (t, *J* = 8.0 Hz, 2H), 1.35 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.5, 116.8, 100.3, 66.2, 40.1, 37.4, 24.8. **FTIR** (neat): υ 3074, 2985, 2932, 2883, 1735, 1637, 1428, 1383, 1223, 1160, 1121, 983, 912, 832 cm^{-1}.

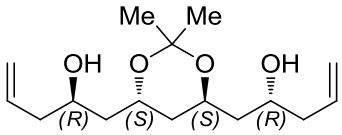
(3*S*,5*S*)-*O*-Isopropylidene-l,7-heptadiol ((*S*,*S*)-3.24)



Ozone was bubbled through a solution of **(*S*,*S*)-3.24a** (53.0 mg, 0.27 mmol) in dichloromethane:methanol (1:1 v/v, 2.7 mL, 0.1 M) at -78 °C until a blue color persisted. The excess O_3 was then purged with argon for 5 min. The reaction was warmed to 0 °C, and $NaBH_4$ (102.0 mg, 2.70 mmol) was added in one portion. The mixture was stirred at room temperature for 3 hr, at which point water (3 mL) was added. The reaction mixture was concentrated and extracted with dichloromethane (5 mL x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2: ethyl acetate to methanol:ethyl acetate, 1:20 with 0.1% triethylamine) provided **(*S*,*S*)-24** (49.0 mg, 0.240 mmol) as a colorless oil in 89% yield.

TLC (SiO_2): R_f = 0.39 (methanol:ethyl acetate, 1:20). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.11-4.04 (m, 2H), 3.76-3.74 (m, 4H), 2.42 (s, 2H), 1.78-1.68 (m, 6H), 1.38 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 100.6, 66.8, 61.1, 38.0, 37.6, 24.9. **FTIR** (neat): υ 3355, 2985, 2941, 2888, 1650, 1383, 1228, 1063, 907, 725 cm^{-1}.

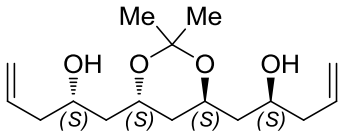
(2*R*,2'*R*)-1,1'-((4*S*,6*S*)-2,2-Dimethyl-l,3-dioxane-4,6-diyl)dipent-4-en-2-ol ((*R*,*S*,*S*,*R*)-3.25)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with [Ir(cod)Cl_2 (6.8 mg, 0.01 mmol), (*R*)-Cl,MeO-BIPHEP (13.7 mg, 0.02 mmol), Cs_2CO_3 (26.2 mg, 0.08 mmol) and 4-chloro-3-nitrobenzoic acid (8.1 mg, 0.04 mmol) was added THF (1.0 mL, 0.2 M) followed by allyl acetate (l00 mg, 1.0 mmol). The reaction mixture was allowed to for 0.5 hr stir at 90 °C and was cooled to room temperature. **(*S*,*S*)-3.24** (40.9 mg, 0.2 mmol) was added and the reaction mixture was allowed to stir for 48 hr at 110 °C, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexane, 1:4 to 1:1, with 0.5% TEA)[8] provided **(*R*,*S*,*S*,*R*)-3.25** (41.8 mg, 0.150 mmol) as a colorless oil in 74% yield and the corresponding mono-allylation product (8.0 mg, 0.030 mmol) as a colorless oil in 16% yield.

TLC (SiO_2): R_f = 0.45 (ethyl acetate:hexane, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.88-5.77 (m, 2H), 5.14-5.10 (m, 4H), 4.20-4.13 (m, 2H), 3.93-3.86 (m, 2H), 2.53 (d, *J* = 4.8 Hz, 2H), 2.26-2.22 (m, 4H), 1.69-1.62 (m, 6H), 1.37(s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.8, 117.8, 100.7, 67.7, 64.4, 42.0, 41.3, 37.7, 24.8. **FTIR** (neat): υ 3413, 3070, 2990, 2941, 2919, 2852, 2358, 2331, 1642, 1379, 1219, 992, 912, 729 cm^{-1}.

(2*S*,2'*S*)-l,l'-((4*S*,6*S*)-2,2-Dimethyl-l,3-dioxane-4,6-diyl)dipent-4-en-2-ol ((*S*,*S*,*S*,*S*)-3.25)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with [Ir(cod)Cl_2 (6.8 mg, 0.01 mmol), (*S*)-Cl,MeO-BIPHEP (13.7 mg, 0.02 mmol), Cs_2CO_3 (26.2 mg, 0.08 mmol) and 4-chloro-3-nitrobenzoic acid (8.1 mg, 0.04 mmol) was added THF (1.0 mL, 0.2 M) followed by allyl acetate (l00 mg, 1.0 mmol). The reaction mixture was allowed to stir for 0.5 hr at 90 °C and

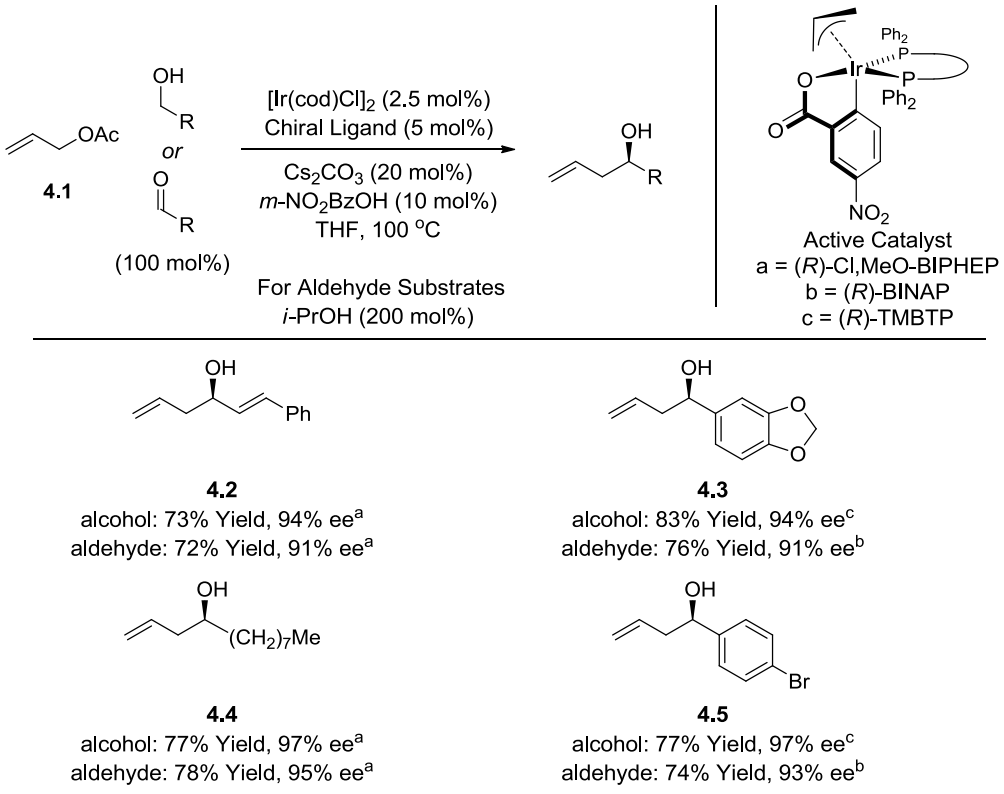
was cooled to room temperature. **(*S*,*S*)-3.24** (40.9 mg, 0.2 mmol) was added and the reaction mixture was allowed to stir for 48 hr at 110 °C, at which point the reaction mixture was evaporated onto silica gel. Purification of the residue by column chromatography (SiO_2: ethyl acetate:hexane, 1:4 to 1:1, with 0.5% TEA)[8] provided **(*S*,*S*,*S*,*S*)-3.25** (46.0 mg, 0.16 mmol) as a colorless oil in 81% yield, and the corresponding mono-allylation product (5.8 mg, 0.023 mmol) as a colorless oil in 12% yield.

TLC (SiO_2): R_f = 0.50 (ethyl acetate:hexane, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.88-5.78 (m, 2H), 5.12-5.07 (m, 4H), 4.11-4.04 (m, 2H), 3.86-3.80 (m, 2H), 3.30 (s, 2H), 2.28-2.16 (m, 4H), 1.69-1.55 (m, 6H), 1.39 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.7, 117.5, 100.8, 71.0, 67.7, 41.9, 41.6, 38.8, 24.9. **FTIR** (neat): υ 3430, 3070, 2985, 2936, 2914, 2848, 1646, 1428, 1375, 1223, 1161, 1116, 1085, 996, 907 cm^{-1}.

Chapter 4: Progress in Iridium Catalyzed Transfer Hydrogenation Allylation Reaction: Effects of *β*- and *γ*-Substitution on Carbonyl Coupling from Alcohol and Aldehyde Oxidation Level

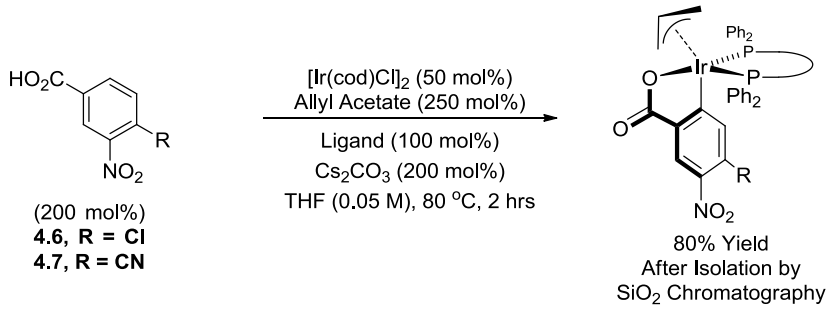
4.1 Background

Under transfer hydrogenation conditions using *ortho*-cyclometallated iridium catalysts generated in situ from allyl acetate, 3-nitrobenzoic acid and a chiral *bis*-phosphine ligand, enantioselective carbonyl allylation is achieved from the alcohol or aldehyde oxidation level using allyl acetate as the allyl donor. Aliphatic, allylic and benzylic alcohols are transformed to the corresponding homoallylic alcohols with uniformly high levels of enantioselectivity. In the presence of isopropanol, but under otherwise identical conditions, aldehydes are converted to an equivalent set of adducts. This protocol avoids cryogenic conditions and the stoichiometric use of metallic reagents or reductants[73] (Scheme 4.1).



Scheme 4.1 Enantioselective iridium catalyzed carbonyl allylation from the alcohol or aldehyde oxidation level.

Our research group find out that the cyclometallated iridium π-allyl *C,O*-benzoate complexes can be pre-formed which have been characterized by single crystal x-ray diffraction and used in transfer hydrogenative coupling with better reactivity than in situ generated conditions. We also found out these catalyst are sufficiently robust that they may be purified chromatographically (Scheme 4.2).[74]



Catalyst R = Cl

(*R*)-I = (*R*)-Cl,MeO-BIPHEP
(*R*)-III = (*R*)-SEGPHOS
(*R*)-V = (*R*)-BINAP
(*rac*)-VII = BIPHEP

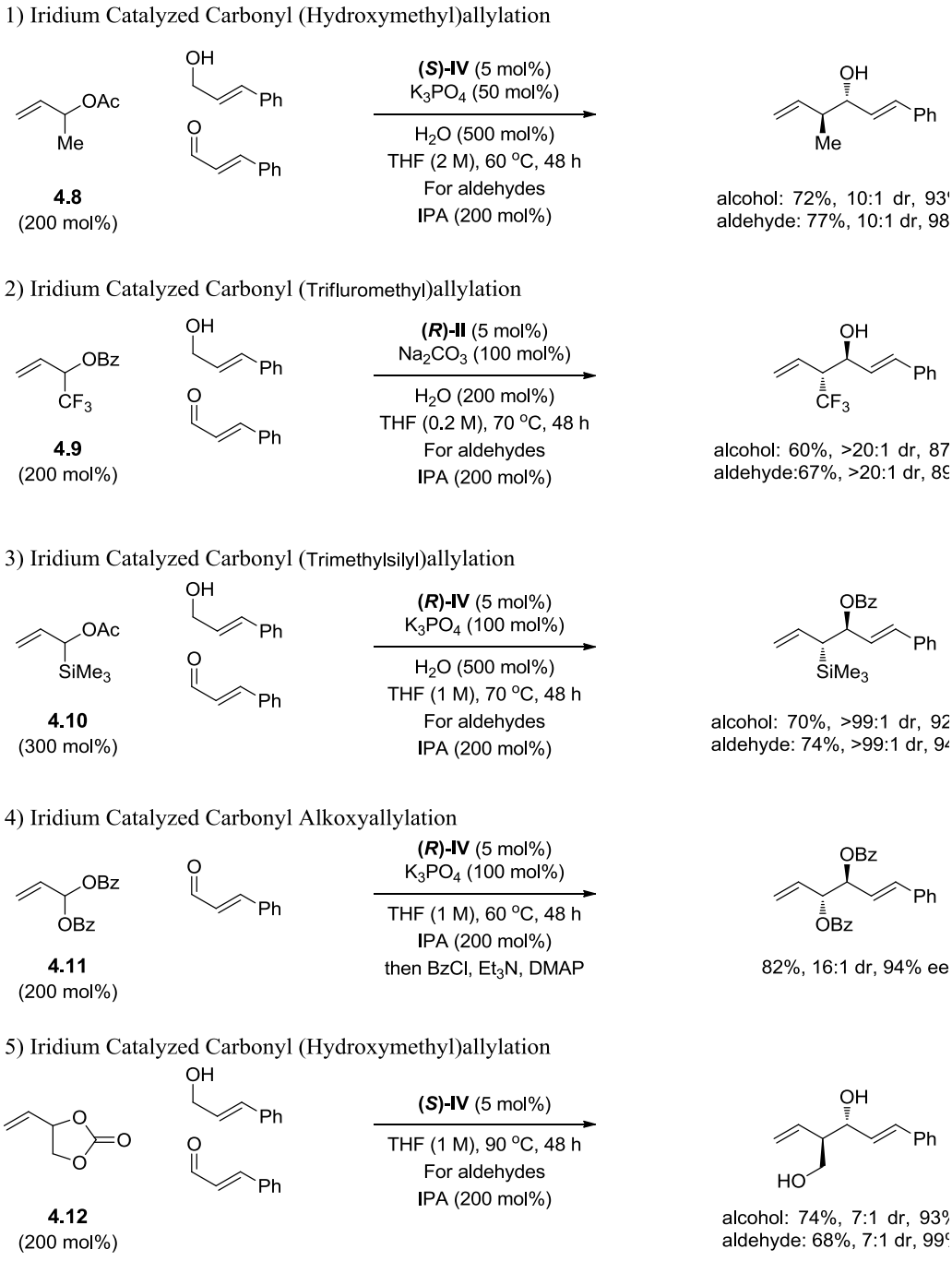
Catalyst R = CN

(*R*)-II = (*R*)-Cl,MeO-BIPHEP
(*R*)-IV = (*R*)-SEGPHOS
(*R*)-VI = (*R*)-BINAP
(*rac*)-VIII = BIPHEP

Scheme 4.2 Synthesis and isolation of iridium cyclometallated catalyst.

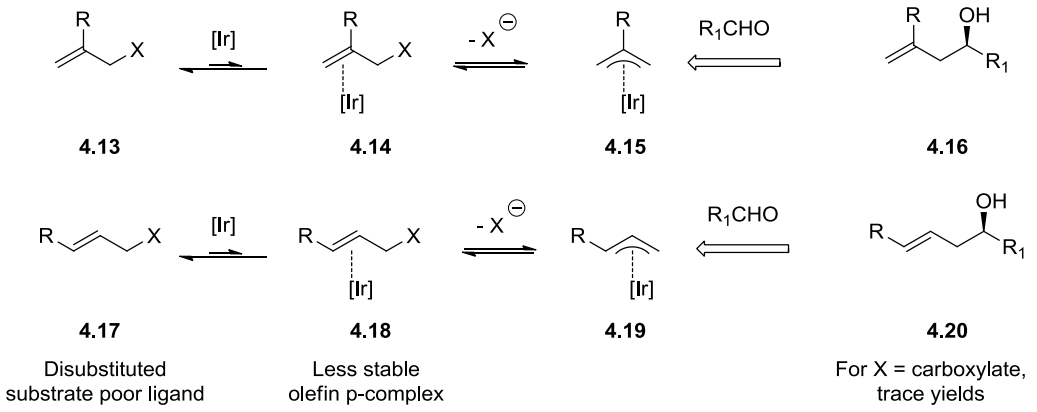
Using the column purified *ortho*-cyclometallated iridium catalysts our research group was able to developed diverse processes beyond allylation. The first important extension relating to this chemistry was enantioselective carbonyl crotylation using α-methyl allyl **4.8** acetate as the crotyl donor. The isolated catalyst enables carbonyl crotylation from alcohol and aldehyde oxidation level at lower temperature (60 ^{o}C) compare to *in situ* generated catalyst (90 ^{o}C) in higher levels *anti*-diseteo- and enantioselecctivity (Scheme 4.3, entry 1).[75] Related processes were established for example, diastereo- and enantioselective α-(trifluromethyl)allylation employing α-trifluoromethyl allyl benzoate **4.9** as allyl donor to get the trifluoroallylation product in high levels of *anti*-diastereo- and enantioselectivity.[76a] Other processes includes, α-(trimethylsilyl)allylation[76b] and α-(hydroxymethyl)allylation[76c] which also have been performed from the alcohol or aldehyde oxidation level (Scheme 4.3, entries 3 and 5). Finally, α-(hydroxy)allylation[76d] was performed using allylic *gem*-dibenzoate **4.11** under the conditions of iridium catalyzed transfer hydrogenation to provide *anti*-1-ene-2,3-diols with excellent relative

and absolute stereocontrol. The latter process can only be performed from aldehyde oxidation level as the alcohol starting material mostly undergoes trans-esterification (Scheme 4.3, entry 4).



Scheme 4.3 Summary of diastereo- and enantioselective allylation methods availed through use of *ortho*-cyclometallated iridium catalysts.

All of the above processes take place by means of substituted π-allyl iridium intermediates results in complete branched regioselectivities, accompanied by good to complete levels of *anti*-diastereoselectivity. This suggested carbonyl addition occurs with allylic inversion from the primary (*E*)-σ-allyl haptomer. Conversely, we believe 1,1- or 1,2-substituent renders the alkene a poor ligand for iridium center and as a result they did not participate in carbonyl addition processes. It has been established that the stability of late transition metal-olefin π-complex decreases with increasing degree of olefin substitution.[77] As olefin coordination is a prerequisite to ionization, the requirement of allyl donors that incorporate monosubstituted olefins likely stems from the shorter lifetime of more highly substituted iridium-olefin π-complexes.The goal of this research was to understand the reactivity pattern of iridium transfer hydrogenation coupling using allylating agents with different higher substitution pattern (Scheme 4.4). In the next two parts of this chapter we will described how we were able to perform transformation using 1,1- or 1,2-substited allylating agent using cyclometallated iridium π-allyl *C,O*-benzoate complexes as catalyst.



Scheme 4.4 Iridium catalyzed allylation reaction is ineffective with 1,1- and 1,2-disubstituted system.

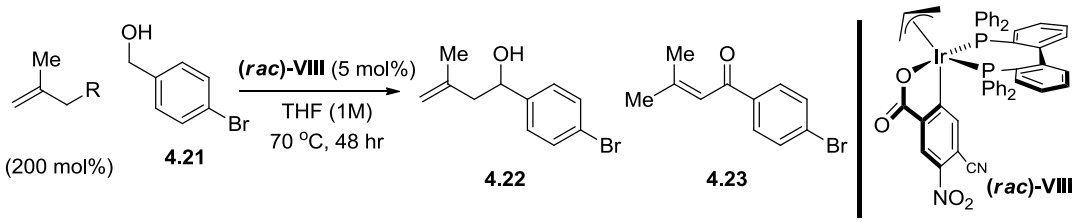
4.2 Part One: 1,1-Disubstituted Olefins as Allyl Donors in Iridium Catalyzed Transfer Hydrogenation Transformation. Enantioselective Grignard Nozaki-Hiyama Methallylation Reaction

4.2.1 Introduction

As indicated in scheme 4.4, higher degree of olefin substitution result in poor coordination ability towards iridium metal center, as a result the ionization prospects. To enable efficient reaction of substituted allyl donors in the absence of any other stabilizing effects, we can compensate for the shorter lifetime of the iridium-olefin π-complex by employing a relative reactive leaving group. Given the paucity of studies devoted exclusively to enantioselective carbonyl methallylation[78,79] it can serve as testing ground for irdium catalyzed carbonyl addition beyond α-substituted allylation.

To test our premise, methallyl acetate, carbonate and sulfonate (**4.24**-**4.27**) were reacted under iridium catalyzed transfer hydrogenation allylation conditions did not participate in carbonyl addition. However, under identical conditions, much higher conversions were observed using methallyl chloride **4.28**, an inexpensive commercial material. Employing **(*rac*)-VIII** as catalyst which is prepared from $[Ir(cod)Cl]_2$, BIPHEP, allyl acetate and 4-cyano-3-nitrobenzoic acid, methylallyl chloride react with benzylic alcohol give rise to methallylation product **4.22** in 72% yield. However, these initial experiments, which were conducted at 70 ^{o}C over 48 hours, also revealed a major side-reaction: oxidation of the initially formed methallylation product **4.22** to form the conjugated dimethyl enone **4.23**. The formation of enone **4.23** corroborates the poor coordinating ability of the methyl-substituted homoallylic olefin which induces β-hydride elimination to form a transient β,γ-enone that isomerizes to the conjugated enone **4.23**.

Table 4.1 Discovery of Iridium catalyzed methallylation reaction using methallyl chloride as allylating agent.

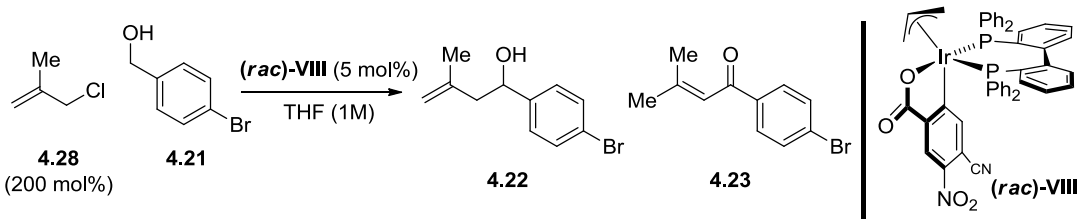


Entry	Leaving Group (R)	Yield (%) **4.22**	**4.23**
1	**4.24,** R = OAc	-	-
2	**4.25,** R = OBz	-	-
3	**4.26,** R = OMs	-	-
4	**4.27,** R = OBoc	-	-
5	**4.28,** R = Cl	72	24

4.2.2 Reaction Optimization

A comprehensive reaction optimization was carried out, varying each facet of reaction conditions. By changing the reaction temperature it was found out that oxidation of the initially formed methallylation product **4.22** to form enone **4.23** can be suppressed at lower temperature (50 ^{o}C) to only 5%, compare to >20% at higher temperature (Table 4.2). However, further reaction optimization was carried out at 70 ^{o}C in order to clearly observe the difference between methallylation and over oxidation product.

Table 4.2 Temperature effect on Iridium catalyzed methallylation.

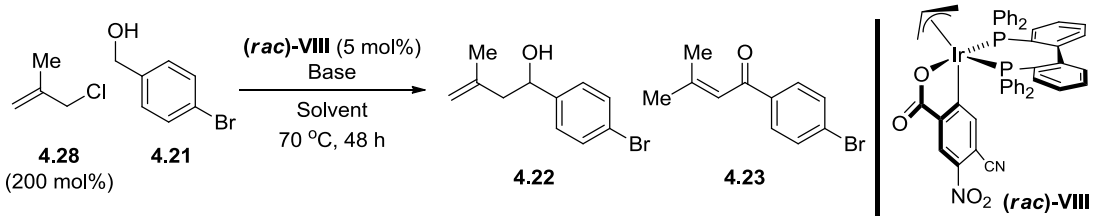


Entry	Temprature (°C)	Yield (%) 4.22	4.23
1	90	73	20
2	80	74	23
3	70	72	24
4	60	67	17
5	50	63	5

Reaction was optimized with the help of Ian Townsend.

Subsequently, we observed effect of reaction solvent, it was found that non-polar solvent like toluene and hexane give practical amount of product but were ineffective in suppressing over oxidation (table 4.3, entries 1 and 2) and chlorinated solvent such as, dichloroethane was likewise not effective (table 4.3, entry 3). On the other hand, oxygenated solvent 1,4-dixane with comparision with THF give rise to low over oxidized side product but with diminished yield. As a result, we use THF as it gave the best conversion among the solvent screened (table 4.3, entries 4 and 5). We looked at different bases and found out that tribasic potassium phosphate was the best than any other organic and inorganic base screen, some of the results are shown in (table 4.3, entries 6,7 and 8).

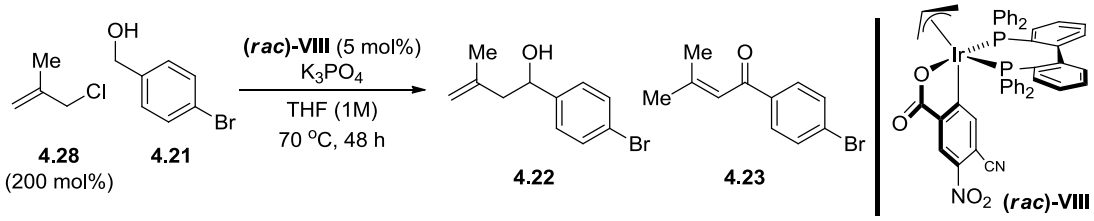
Table 4.3 Solvent and base effect on Iridium catalyzed methallylation reaction.



Entry	Base (100 mol%)	Solvent (1M)	Yield (%) **4.22**	**4.23**
1	K_3PO_4	Tolune	37	15
2	K_3PO_4	Hexane	33	22
3	K_3PO_4	DCE	trace	trace
4	K_3PO_4	Dioxane	59	9
5	K_3PO_4	THF	72	24
6	Na_2CO_3	THF	21	trace
7	NaOAc	THF	trace	trace
8	2,6-Lutidine	THF	trace	trace

It was interesting to note that potassium phosphate was the best as it was effective related chemistry. However, the amount of base also effects the reaction in great yield. Lower amount of potassium phosphate (50 mol% and 75 mol%) resulted in less oxidation product (none and 12%, respectively, table 4.4 entries 2 and 3) nevertheless at the expense of product yield. The initial 100 mol% base loading was optimal loading as higher amount resulted in diminished yield as a result of product decomposition. Methallyl chloride amount was also screen, and higher loadings (300 mol%) suppressed over oxidation to only 16%, higher loading with respect to cost of reaction was not an issue as methyl chloride is very inexpensive. Finally, carrying out the reaction at 50 ^{o}C with 300 mol% methallyl chloride summed up the best reaction condition (Table 4.4, entry 7). Any further optimizations were unsuccessful.

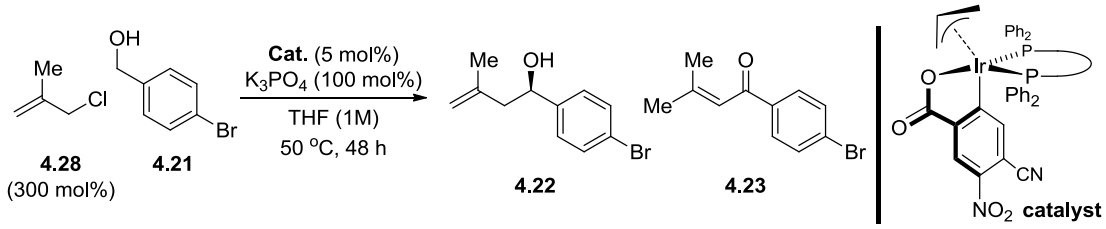
Table 4.4 Effect of K_3PO_4 and methallyl chloride loading on Iridium catalyzed methallylation reaction.



Entry	Methallyl chloride (mol%)	T (°C)	K_3PO_4 (mol%)	Yield (%) **4.22**	**4.23**
1	200	70	50	25	-
2	200	70	75	60	12
3	200	70	100	72	24
4	200	70	125	68	17
5	200	70	150	40	-
6	300	70	100	74	16
7	300	50	100	76	5

With optimal reaction conditions in hands, we look at the enantioselective methallylation. Generally, the chiral *ortho*-cyclometallated iridium *C,O*-benzoates catalyze carbonyl additions are very effective in asymmetric discrimination. Indeed, the reaction carried out with chiral modified catalyst gave excellent enantioselectivity. Catalyst modified by (*R*)-SEGPHOS **(*R*)-IV,** provided the methallylation product **4.22** in 63% and 96% enantiomeric purity accompanied by 32% over oxidized enone product **4.23**. (*R*)-BINAP modified catalyst, **(*R*)-VI** suppress the over oxidation but resulted in lower enantioselectivity (85% ee). Since (*R*)-BINAP is readily available inexpensive and highly desirable ligand, yet, we were not able to improve the enantioselectivity by changing the reaction conditions. Finally, with (*R*)-Cl,MeO-BIPHEP ligated catalyst **(*R*)-II**, we were able to retain high enantioselectivity (94% ee) and highly practical yield (84%) accompanied with small amount (12%) of over oxidized product. Meanwhile, we also found out that the chiral catalyst **(*R*)-II** was more effective in methallylation reaction than **(*rac*)-VIII,** we were able to get comparable yields using shorter the reaction time (24 h). In other substrates, shorter reaction time was helpful in suppressing over oxidation (table 4.5).

Table 4.5 Enantioselective Iridium catalyzed methallylation reaction, screening of chiral ligands.



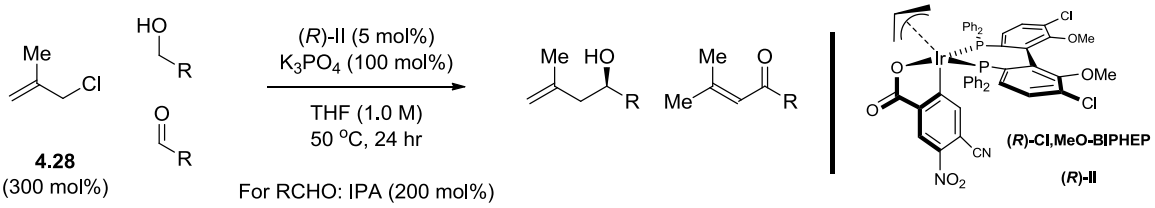
Entry	Ligand-catalyst	Time (h)	Yield 4.22	4.23
1	(*R*)-SEGPHOS-(***R*)-IV**	48	63%, 96% ee	32%
2	(*R*)-BINAP-(***R*)-VI**	48	84%, 85% ee	14%
3	(*R*)-Cl,MeO-BIPHEP-(***R*)-II**	48	84%, 94% ee	12%
4	(*R*)-Cl,MeO-BIPHEP-(***R*)-II**	24	83%, 96% ee	12%

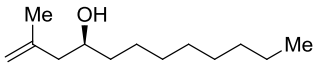
4.2.3 Substrate Scope

Under these optimal conditions including catalyst **(*R*)-II** (5 mol%), methallyl chloride (300 mol%) and potassium phosphate (100 mol%) in THF (1 M) at 50 ^{o}C the reaction displayed very general reactivity. Benzylic alcohols were transformed to the desired methallylation product in good yields, beside the 4-bromobenzyl alcohol, piperonyl alcohol resulted in 78% isolated yield of product **4.31** and 95% enantiomeric excess. Heteroaryl alcohol 2-benzotheinyl alcohol gave methallylation product **4.37** in 87% and 96% enantiomeric excess. These conditions were applied to aliphatic alcohols, nonanol, mono-protected propanediol and neopentyl alcohol resulted in the corresponding products of methallylation (**4.29, 4.32 and 4.35,** respectively) in good to excellent yields and with uniformly high levels of enantioselectivity. The aliphatic alcohols were particularly well behaved substrates in view of their ability to undergo methallylation to form adducts with virtually complete suppression of further oxidation to form enones. The same is true for cyclohexane methanol. On the hand, allylic alcohols undergo competing enone formation more evidently much like benzylic alcohols which are more susceptible to β-hydride elimination. To suppress over oxidation in allylic systems, the reaction of cinnamyl alcohol and geraniol reactions were carried out with additional 200 mol% isopropanol to give the products **4.33** and **4.36** in 80% yield. In the presence of isopropanol (200

mol%), but under otherwise identical conditions an equivalent set of adducts can be generated from aldehydes. In most cases, comparable isolated yields and enantioselectivities are observed. Thus, carbonyl Grignard-Nozaki-Hiyama methallylation is achieved with equal facility from the alcohol or aldehyde oxidation level (table 4.6).

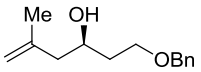
Table 4.6 Substrate scope of Iridium catalyzed methallylation reaction.





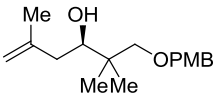
4.29

Alchol:	80% Yield (>1% enone), 95% ee
Aldehyde:	75% Yield (>1% enone), 97% ee



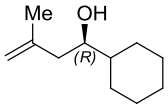
4.32

Alchol:	69% Yield (>1% enone), 96% ee
Aldehyde:	55% Yield (>1% enone), 95% ee



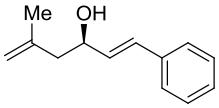
4.35

Alchol:	90% Yield (>1% enone), 94% ee[c]
Aldehyde:	91% Yield (>1% enone), 97% ee[c]



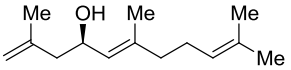
4.30

Alchol:	72% Yield (>1% enone), 92% ee
Aldehyde:	74% Yield (>1% enone), 91% ee



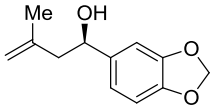
4.33

Alchol:	80% Yield (12% enone), 94% ee[a,c]
Aldehyde:	82% Yield (13% enone), 95% ee[b,c]



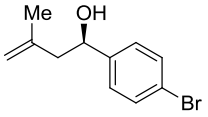
4.36

Alchol:	80% Yield (>1% enone), 94% ee[a,c]
Aldehyde:	75% Yield (6% enone), 93% ee[b,c]



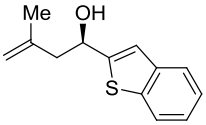
4.31

Alchol:	78% Yield (5% enone), 95% ee[c]
Aldehyde:	85% Yield (10% enone), 96% ee[c]



4.34

Alchol:	83% Yield (14% enone), 96% ee
Aldehyde:	90% Yield (8% enone), 95% ee



4.37

Alchol:	87% Yield (5% enone), 96% ee[c]
Aldehyde:	91% Yield (5% enone), 95% ee[c]

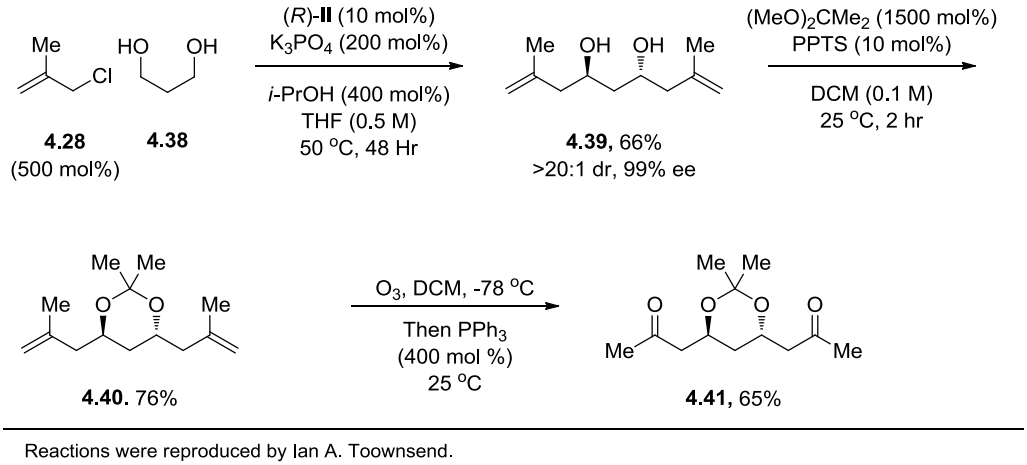
[a] Reaction was carried out with 200 mol% IPA. [b] Reaction were carried out with 400 mol% IPA.[c] Reaction were performed by Ian A. Toownsend.

The absolute stereochemistry of methallylation products was made in analogy to that determined for bromide containing adduct **4.34** by single crystal X-ray diffraction analysis using the anomalous dispersion method.

4.2.4 Bis-methallylation of 1,3-Propanediol

To showcase the utility of this methodology, double enantioselective methallylation of

1,3-propanediol **4.38** was attempted under standard conditions. The corresponding C_2-symmetric diol **4.39** is produced in 66% isolated yield as a single enantiomer, as the minor enantiomer of the mono-adduct is transformed to the *meso*-stereoisomer of the product. Diol **4.39** was converted to acetonide **4.40** and subjected to ozonolysis to provide the formal product of double acetone aldol addition **4.41** (Scheme 4.5).



Scheme 4.5 Bis-methallylation of 1,3-propanediol and synthesis of C_2-symmetric bis-acetone adduct.

4.2.5 Summary

In summary, we found out that methallyl acetate does not serve as an efficient allyl donor due to the lower stability and, therefore, shorter lifetime of the iridium-olefin π-complex that precedes formation of the requisite π-allyliridium complex. Through the use of more reactive leaving group in methallyl chloride, the ionization to form the π-allyliridium complex is more rapid, hence compensating for the shorter lifetime of the more highly substituted olefin π-complex. Based on this insight into the requirements of the catalytic process, highly enantioselective Grignard-Nozaki-Hiyama methallylation is achieved from the alcohol or aldehyde oxidation levels in the absence of stoichiometric metallic reagents or reductants. Further, double enantioselective methallylation of 1,3-propanediol was carried out in good yield to obtained C_2-symmetric bis-methallylation product as a single enantiomer, as the minor enantiomer of the mono-adduct is transformed to the *meso*-stereoisomer of the product.

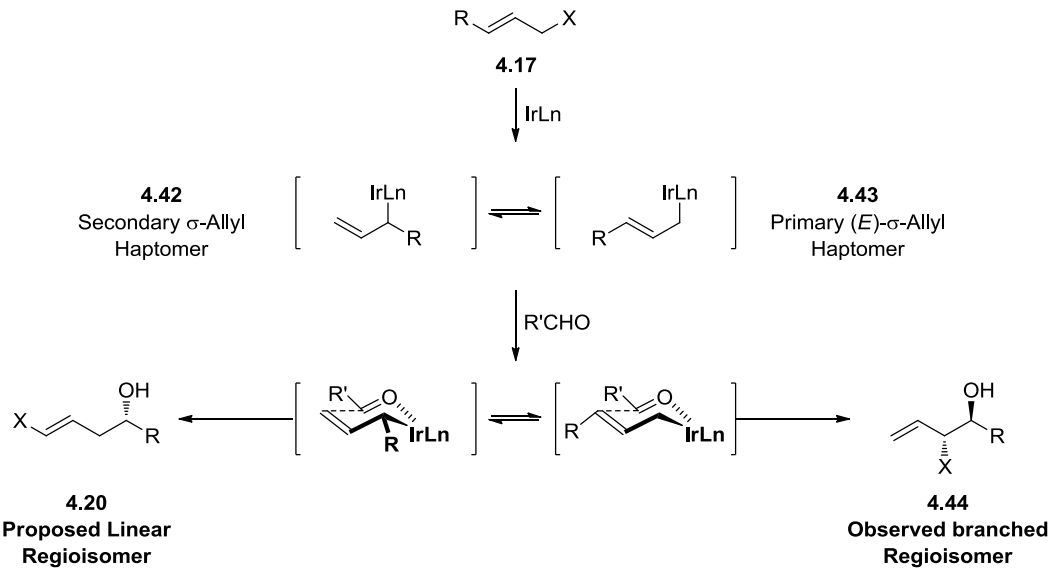
4.3 Part Two: 1,2-Disubstituted Olefins as Allyl Donors in Iridium Catalyzed Transfer Hydrogenation Transformation. Enantioselective Vinylogous Aldol-Reformatsky Addition

4.3.1 Introduction

Vinylogues of the aldol reaction represent an important class of carbonyl addition processes.[80] The vast majority of enantioselective vinylogous aldol additions employ dienolates and dienol ethers derived from β-ketoester esters[81] in combination with chiral Lewis acids,[80a-k] chiral Lewis bases[80k-m] or chiral H-bond donors.[80n] Dienolates and dienol ethers derived from simple α,β-unsaturated carbonyl compounds[75k-m,76] and 2-siloxy furans[82] also participate in enantioselective vinylogous aldol additions. While excellent regio- and enantioselectivities have been obtained in certain cases, the formation and tractability of the requisite dienol ethers pose a barrier to their use. Additionally, chiral Lewis acid catalyzed reactions of silyl dienol ethers often suffer from competing racemic silyl cation catalyzed background reactions, requiring slow addition of the dienol ether, cryogenic conditions and high catalyst loadings. Vinylogous direct aldol additions of unmodified α,β-unsaturated carbonyl compounds potentially address these limitations,[83] however, to date, such transformations are restricted to the use of 2-(5H)-furanones as aldol donors. In a significant departure from prior art, Shibasaki and Kanai devised a *reductive* vinylogous aldol reaction of allenic esters mediated by pinacolborane.[84] A related reductive process, the vinylogous Reformatsky reaction, could potentially deliver identical products, however, enantioselective variants are unknown.

As deliberated in the beginning of this chapter, we have found that chiral *ortho*-cyclometallated iridium *C,O*-benzoates catalyze carbonyl transformations take place by way of substituted π-allyl iridium intermediates, resulted in complete branched regioselectivities, accompanied by good to complete levels of *anti*-diastereoselectivity, suggesting carbonyl addition occurs with allylic inversion from the primary (*E*)-σ-allyl haptomer. We discussed the degree of olefin substitution result in interference between iridium and olefin and hence, decrease the ionization prospects of allylating agent. We also discussed, how a better leaving group enabled us to perform transformation with 1,1-disubstituted olefin in allylating agent.

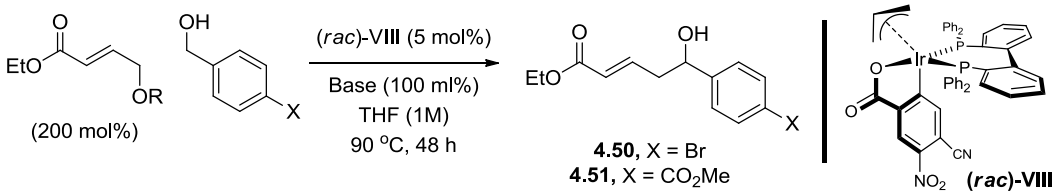
For 1,2-disubstituted system, the linear carbonyl addition products might be availed upon stabilization of the secondary σ-allyl haptomer through introduction of a stabilizing effect. Introduction of carbonyl moiety can stablize the secondary σ-allyl haptomer, equivalent to a η^1-*C*-bound iridium enolate.[85]



Scheme 4.6 Differential π-allyl stabilization by substituent X may lead to new reactivity pattern.

The veracity of this analysis is borne out by the exposure of the γ-acyloxy crotonate **4.45** to benzyl alcohol **4.21** in the presence of the *ortho*-cyclometallated iridium *C,O*-benzoate complex modified by BIPHEP, designated as **(*rac*)-VIII.** While potassium phosphate was used as base and the products of carbonyl addition was obtained in 15% yield. The more labile benzoate ester **4.46** leads to slight improvement in yield. Though, due to practical problem of product isolation further optimizations were carried out with metyl 4-(hydroxymethyl)benzoate **4.49**. Pivaloyl crotonate **4.47** on the other hand did not participate in coupling reaction. However, to our delight *tert*-butyl carbonate **4.48** of γ-hydroxy crotonate resulted in 26% isolated yield. The Boc-carbonate **4.48** is better allylating agent as it did not participate in acyl transfer reaction neither the reaction required any external base (Table 4.7).

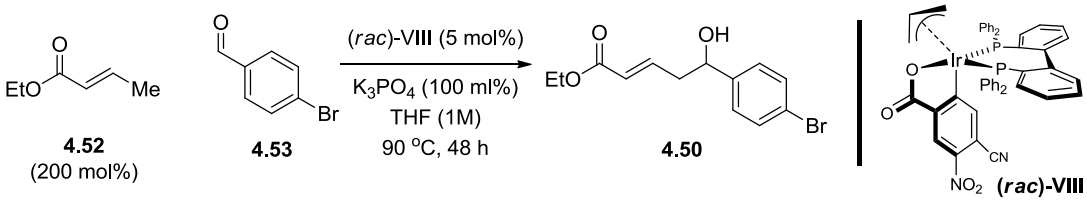
Table 4.7 Discovery of vinylogous aldol reaction and screening of effect of leaving group on reactivity.



Entry	R	X	Base (100 mol%)	Yield (%)
1	**4.45**, R = Ac	**4.21**, X = Br	K_3PO_4	15
2	**4.46**, R = Bz	**4.21**, X = Br	K_3PO_4	22
3	**4.46**, R = Bz	**4.49**, X = CO_2Me	K_3PO_4	16
4	**4.47**, R = Piv	**4.49**, X = CO_2Me	K_3PO_4	-
5	**4.48**, R = Boc	**4.49**, X = CO_2Me	-	26

Before we carried out an extensive reaction optimization, it was suspected that the product of vinylogous Reformatsky-aldol addition might be formed as a base catalyzed background reaction of ethyl crotonate, which might have produced from γ-acyloxy crotonate reduction. Control experiments were performed where ethyl crotonate **4.52** was exposed to otherwise similar reaction conditions deprived of any addition product (table 4.8).

Table 4.8 Control vinylogous aldol addition reaction.

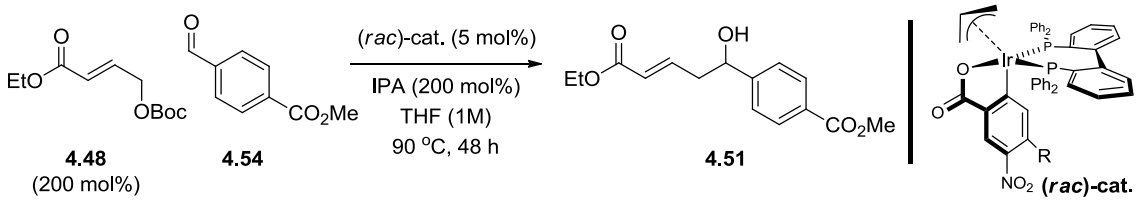


Entry	Catalyst	Additive (100 mol%)	Yield (%)
1	(*rac*)-VII	IPA	-
2	-	IPA	-
3	-	-	-

4.3.2 Reaction Optimization

We started optimization by changing the electronic character of *ortho*-cyclometallated iridium *C,O*-benzoate complex, by means of changing the substituent at 4-position of the benzoic acid. The reactivity pattern was not very different from electron donating to withdrawing group, however, electron withdrawing substituent give uniformly good reactivity. The 4-chloro-3-nitrobenzoate based catalyst **(*rac*)-VII** was chosen for any further reaction optimization due to readily availability and well behaved reactivity pattern (Table 4.9, entry 6).

Table 4.9 Iridium *C,O*-benzoate complex modified, effects on vinylogous aldol reaction.



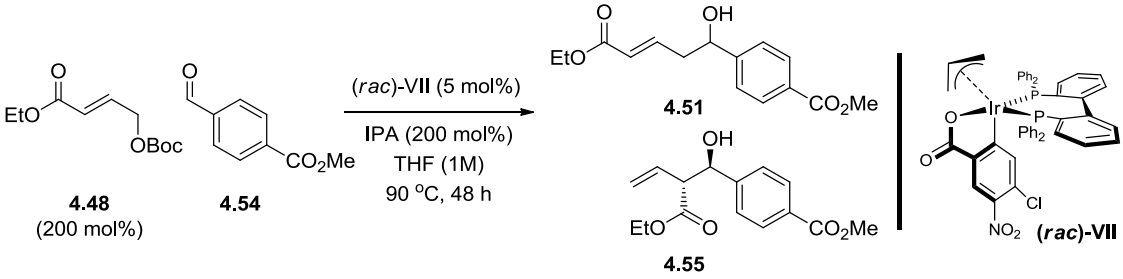
4.48 (200 mol%) **4.54** **4.51**

Entry	R	Yield (%)	Entry	R	Yield (%)
1	MeO	36	5	CF_3	42
2	H	17	6	Cl	40
3	CN	30	7	F	41
4	NO_2	39	8	Br	39

Reaction was optimized with the help of Jason R. Zbieg.

However, observing the reaction temperature, it was found that at lower temperature the vinylogous Reformatsky-aldol addition suffer from regioselectivity issues. At lower temperature, the primary (*E*)-δ-allyl haptomer (Scheme 4.6) is the reactive specie, which resulted in the observed branched selectivity by α-addition of the enolate to aldehyde. However, at higher temperature the secondary *δ*-allyl haptomer is more reactive giving rise to novel linear selectivity by virtue of *γ*-addition. This reactivity pattern suggests a Curtin-Hammett scenario wherein the equilibrating mixture of primary and secondary *σ*-allyl haptomers selectively reacts with aldehyde at different temperature. We were mostly interested in the new reactivity character and further optimized the linear *γ*-addition product.

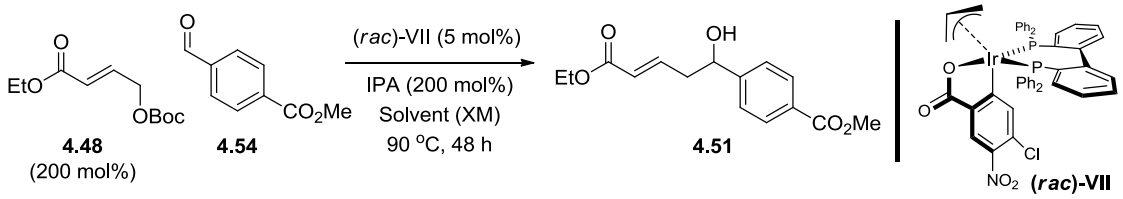
Table 4.10 Temperature and regionselectivity correlation in Iridium catalyst vinylogous aldol reaction.



Entry	Temperature (°C)	Yield (%) **(4.51:4.55)**
1	90	40 (>20:1)
2	85	46 (>10:1)
3	80	71 (3:1)
4	75	70 (1.5:1)
5	70	72 (1:1)

It was found out that the reaction works better at lower concentration and 0.5 M was superior than 1 M (48% and 40%, respectively, table 4.11). The solvent screen was very interesting and it was found out that chlorinated solvent dichlorethane was not as effective. Toluene was slight better than THF and 2-methyltetrahydrofuran, but 1,4-dioxane was the best among the solvents (Table 4.11, entry 8).

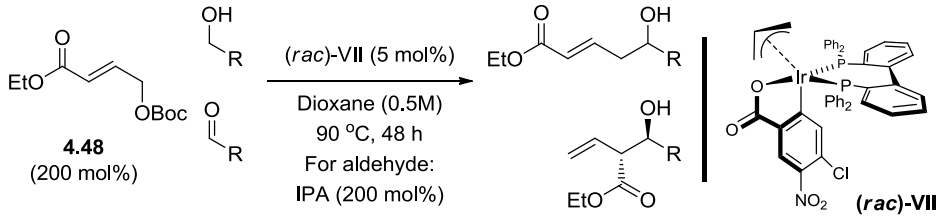
Table 4.11 Reaction solvent and concentration effect on Iridium catalyst vinylogous aldol reaction.

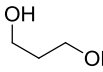
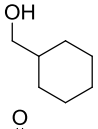
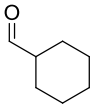


Entry	Conc. (THF M)	Yield (%)	Entry	Solvent (1M)	Yield (%)
1	0.25	45	5	DCE	34
2	0.5	48	6	Toluene	42
3	1	40	7	2-Me-THF	37
4	2	38	8	Dioxane	46

As we have discussed, benzylic alcohol have resulted in indiscriminate regioselectivity, it was interesting to look at aliphatic example. To find out substrate-regioselectivity relationship, *O*-4-methoxybenzyl-1,3-propanediol **4.56**, cyclohexanemethanol **4.58** and corresponding aldehyde (**4.57** and **4.59,** respectively) were examined under optimized condition. The former *O*-4-methoxybenzyl-1,3-propanediol **4.56**, was found to be completely unselective towards regioselectivity giving the product in equal amount of regioselectivity however, the corresponding aldehyde was slightly favorable to linear product (2:1 rr). Conversely, by increasing the steric hindrance at the reactive carbonyl center, as by α-substitution in cyclohexanemethanol **4.58** the reacted to deliver the product in higher level of linear regioisomer (4:1 rr). The corresponding aldehyde gave slightly better selectivity (5:1) (Table 4.12). Any further optimization to improve regioselectivity was unsuccessful.

Table 4.12 Aliphatic alcohol in Iridium catalyst vinylogous aldol reaction. Regioselectivity effect due to α-substitution and oxidation state of starting material.

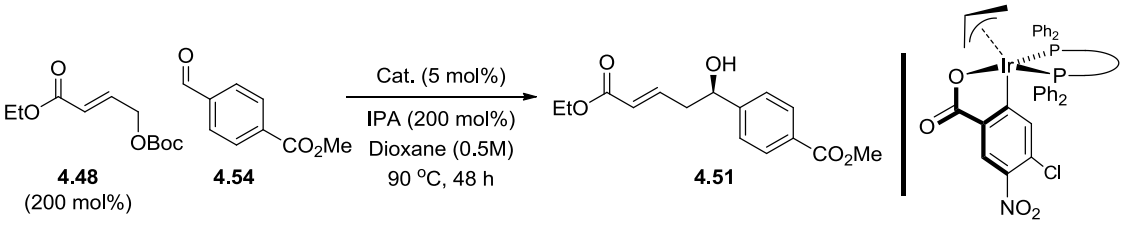


Entry	Substrate		Yield (%) (linear:branched)
1		**4.56**	89 (1:3.3)
2		**4.57**	50 (2:1)
3		**4.58**	65 (4:1)
4		**4.59**	80 (5:1)

4.3.3 Enantioselective Vinylogous Reformatsky Aldol Reaction

In spite of regioselectivity limitation, the enantioselective coupling was desirable. Screening of Chiral catalyst were performed however, most of the chiral catalyst resulted in poor enantioselectivity. (*R*)-Cl,MeO-BIPHEP modified catalyst, **(*R*)-I** was the best catalyst in the series (Table 4.13, entry 5). Excitingly, for the same reaction conditions, it was noted that the enantioselectivity was slightly higher for shorter reaction time. This anomaly can be explained by invoking oxidation reduction of the coupling product which results in scrambling of enantiomeric purity. This analysis bode with assumption that the additional substituent on double bond of the product renders it poor coordinating ability which in turn makes it susceptible to iridium catalyzed *β*-hydride elimination. Since, the benzylic alcohols are more reactive towards *β*-hydride elimination and therefore, would give poor enantiomeric excess. However, aliphatic alcohols and un-activated allylic and benzylic substrate can potentially provide better enantioselectivity.

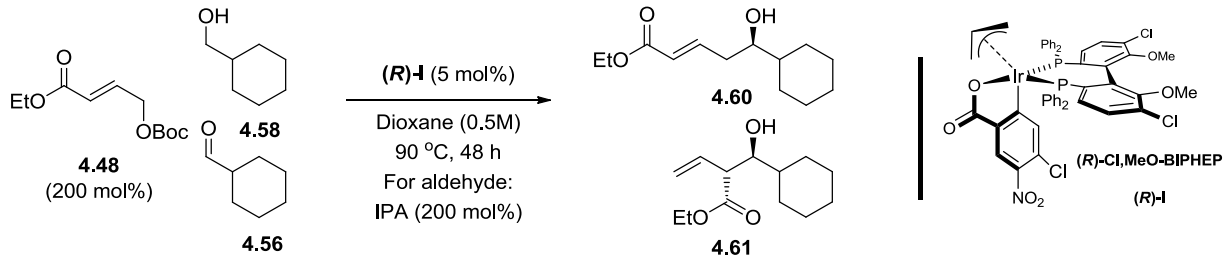
Table 4.13 Ligand screen in asymmetric vinylogous aldol reaction.



Entry	Ligand	Yield (%)	% ee
1	BIPHEP **(rac)-VII**	60	-
2	(*R*)-SEGPHOS **(*R*)-III**	49	31
3	(*R*)-DTBM-SEGPHOS	-	-
4	(*R*)-BINAP **(*R*)-V**	5	46
5	**(*R*)-Cl,MeO-BIPHEP (*R*)-I**	**64**	**53**

As discussed above, the hypothesis was put to test when cyclohexanemethanol was use as substrate in enantioselective vinylogous Reformatsky addition reaction, which resulted in good yield, regio- and excellent enantioselectivity employing either alcohol or aldehyde oxidation level (table 4.14).

Table 4.14 Enantioselective vinylogous aldol addition in cyclohexanemethanol and cyclohexanecarboxaldehyde.

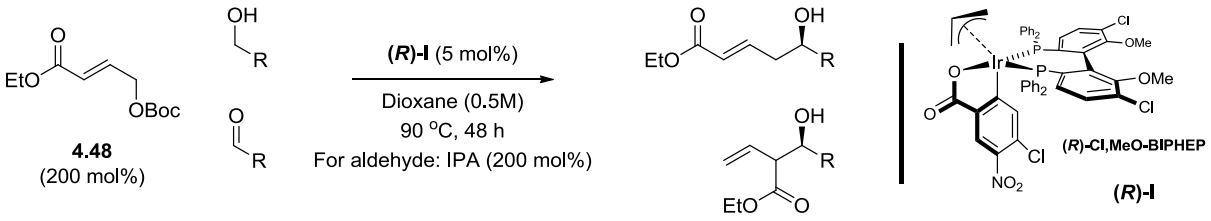


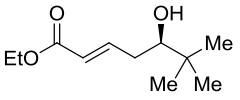
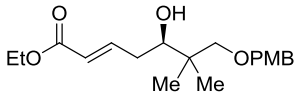
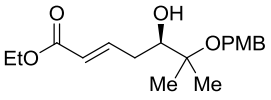
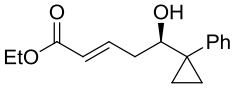
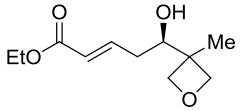
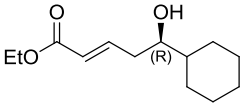
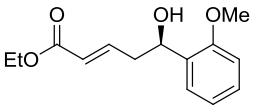
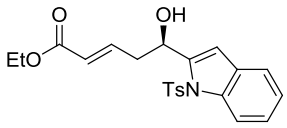
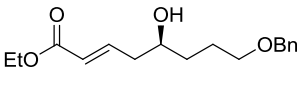
Entry	Substrate	Yield (%) (**4.60**:**4.61**)	(% ee) (**4.60**)
1	**4.58**	77 (5:1)	95
2	**4.59**	88 (6:1)	92

4.3.4 Substrate Scope

Diverse range of substrate was screen to examine the scope of enantioselective vinylogous Reformatsky-aldol addition. Similar to cyclohexanemethanol, in the presence of the chiral *ortho*-cyclometallated iridium *C*,*O*-benzoate complex modified by (*R*)-Cl,MeO-BIPHEP, [2,2'-bis(diphenylphosphino)-5,5'-dichloro-6,6'-dimethoxy-1,1'-biphenyl], designated as **(*R*)-I**, *O*-benzyloxypropanediol undergo carbonyl addition giving rise to mixture of regioisomer in a combined 87% yield as a 1:2 mixture of linear (88% ee) and branched regioisomers, favoring formation of the branched adduct. However, primary neopentyl alcohols deliver products of C-C coupling with complete linear regioselectivity and exceptional enantioselectivity. In all cases, roughly equivalent yields and selectivities are observed when the C-C coupling is performed using aldehydes. Finally, benzylic alcohols and the corresponding aldehydes engage in C-C coupling to furnish adduct **4.64, 4.67** and **4.69** in good yield. Here, as suggested, slight erosion in optical purity of is observed over the course of the reaction, due to reversible oxidation-reduction of the secondary benzylic alcohol product (Table 4.15).

Table 4.15 Substrate scope of enantioselective vinylogous Reformatsky-aldol addition from the alcohol or aldehyde oxidation level.



			
	4.62	**4.65**[a]	**4.68**[a]
Alcohol:	59%, > 20:1 rr, 96% ee	75%, > 20:1 rr, 99% ee	88%, > 20:1 rr, 96% ee
Aldehyde:	85%, > 20:1 rr, 96% ee	83%, > 20:1 rr, 99% ee	70%, > 20:1 rr, 99% ee
			
	4.63	**4.66**	**4.60**
Alcohol:	70%, > 20:1 rr, 97% ee	61%, > 20:1 rr, 90% ee	77%, 5:1 rr, 95 % ee
Aldehyde:	60%, > 20:1 rr, 93% ee	58%, > 20:1 rr, 93% ee	88%, 6:1 rr, 92 % ee
			
	4.64[a]	**4.67**	**4.69**
Alcohol:	80%, > 20:1 rr, 86% ee	80%, 5:1 rr, 95% ee	87%, 1:2 rr, 88% ee
Aldehyde:	80%, > 20:1 rr, 94% ee	94%, 5:1 rr, 96% ee	65%, 2:1 rr, 83% ee

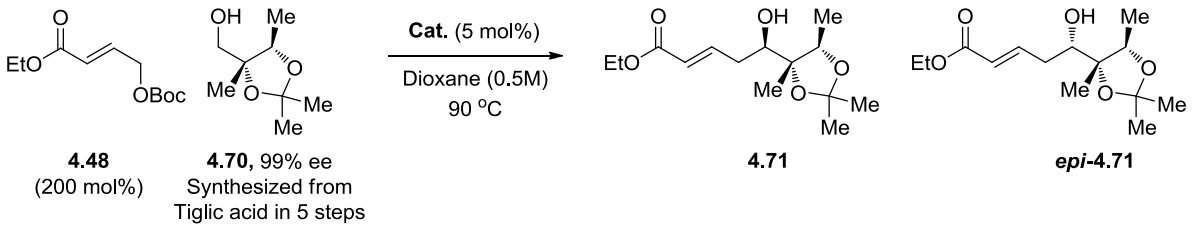
[a]Reaction were conducted by Jason R. Zbieg.

Linear regioselectivity in response to increased steric demand of the aldehyde suggests a Curtin-Hammett scenario wherein carbonyl addition occurs selectively from an equilibrating mixture of primary and secondary σ-allyl haptomers.[86] Beyond electronic effects, it is likely that carbonyl addition from the *α*-C-bound iridium enolate to form the less substituted C-C bond is favored due to the absence of gauche interactions in the transition state. For sterically demanding aldehydes, such gauche interactions would be accentuated, thus increasing the preference for the linear regioisomer.

4.3.5 Catalyst-directed Vinylogous Reformatsky-aldol Addition

To further explore the scope of the vinylogous Reformatsky-aldol addition, catalyst-directed diastereoselectivity was explored in the coupling of allylic carbonate **4.48** to α-chiral alcohol **4.70**.[87] Under standard conditions employing **(*R*)-I** as precatalyst, the linear adduct **4.71** was isolated as a single regio- and stereoisomer. Using the enantiomeric precatalyst **(*S*)-I**, the linear adduct ***epi*-4.71** is isolated as a single regio- and stereoisomer. Thus, complete levels of catalyst-directed diastereoselectivity are observed. In contrast, using the analogous achiral iridium complex modified by BIPHEP, (2,2'-bis(diphenylphosphino)biphenyl), diastereomers **4.71** and ***epi*-4.71** are produced in 58% yield in a 1:1.5 ratio, respectively, along with a 9% yield of the branched regioisomer (Table 4.16).

Table 4.16 Catalyst-directed diastereoselectivity in vinylogous Reformatsky-aldol addition from the alcohol oxidation level.



4.48 (200 mol%)

4.70, 99% ee Synthesized from Tiglic acid in 5 steps

4.71

***epi*-4.71**

Entry	Ligand, Catalyst	Time (hr)	Yield **4.71**:***epi*-**4.71**
1	(*R*)-Cl,MeO-BIPHEP, **(*R*)-I**	72	68%, >20:1 dr >20 : 1 rr
2	BIPHEP, **(*rac*)-VII**	48	67% 1:1.5 dr 7:1 rr
3	(*S*)-Cl,MeO-BIPHEP, **(*S*)-I**	48	56%, 1:>20 dr >20 : 1 rr

4.3.6 Summary

In this study we report a catalytic method for enantioselective vinylogous Reformatsky-type aldol addition in which asymmetric carbonyl addition occurs with equal facility from the alcohol or aldehyde oxidation level. Good to excellent levels of regioselectivity and uniformly high levels of enantioselectivity were observed across a range of alcohols and aldehydes.

Additionally, exceptional levels of catalyst-directed diastereoselectivity may be achieved. Insight into the structural-interactional features of the catalytic system *via* partitioning of linear and branched adducts suggests a Curtin-Hammett scenario, wherein carbonyl addition occurs selectively from an equilibrating mixture of primary and secondary σ-allyl haptomers. The collective data are consistent with carbonyl addition from the secondary α-*C*-bound iridium enolate to form the less substituted C-C bond due to the absence of gauche interactions in the transition state. Notably, in reactions conducted from the alcohol oxidation level, the only stoichiometric byproducts formed are carbon dioxide and *tert*-butanol.

4.4 Experimental Section

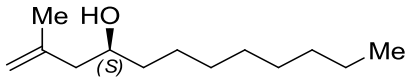
4.4.1 Part One: 1,1-Disubstituted Olefins as Allyl Donors in Iridium Catalyzed Transfer Hydrogenation Transformation. Enantioselective Grignard Nozaki-Hiyama Methallylation Reaction

4.4.1 Representative Synthesis of Catalyst: Synthesis of (*R*)-II

To a mixture of $[Ir(cod)Cl]_2$ (134.3 mg, 0.20 mmol, 100 mol%), (*R*)-Cl,MeO-BIPHEP (260.6 mg, 0.40 mmol, 200 mol%), Cs_2CO_3 (260.6 mg, 0.80 mmol, 400 mol%), 4-Cl-3-NO_2BzOH (161.2 mg, 0.89 mmol, 400 mol%) and allyl acetate (100.1 mg, 1.0 mmol, 500 mol%) in a sealed tube under N_2 atmosphere was added THF (4.0 mL, 0.05 M). The reaction mixture was stirred for 30 min at ambient temperature and heated for 1.5 hr at 80 ^oC, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered and washed with THF (10 mL). The filtrate was concentrated *in vacuo* and purified by flash column chromatography (dichloromethane:ether, 3:1). The purified catalyst was precipitated from THF (2 mL) and hexane (50 mL) to give a yellow precipitate, which was collected by filtration and dried under vacuum to provide **(*R*)-II** (344.0 mg, 0.320 mmol) in 80% yield.

4.4.2 Experiment details of Methallylation from Alcohol Oxidation Level

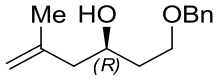
(S)-2-methyldodec-1-en-4-ol (4.29)



To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), alcohol **4.29a** (28.5 mg, 0.20 mmol, 100 mol%) and β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^oC and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:40 to 1:20) provided the desired product **4.29** (31.7 mg, 0.160 mmol) as a colorless oil in 80% yield.

TLC (SiO_2): R_f = 0.38 (ethyl acetate: hexanes, 1:9). **[α]$_D^{25}$** = -8.0 (c = 1, CH_2Cl_2), literature value for *ent* **3a**, +11.2 (c = 3.02, CCl_4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.90-4.87 (m, 1H), 4.81-4.78 (m, 1H), 3.75-3.68 (m, 1H), 2.21 (dd *J* = 13.5, 3.3 Hz, 1H), 2.08 (ddd, *J* = 13.7, 9.4, 0.7 Hz, 1H), 1.76 (s 3H), 1.68 (d, *J* = 1.7, 1H), 1.46-1.27 (m, 14H), 0.88 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 142.9, 113.4, 68.6, 46.2, 37.1, 31.9, 29.7, 29.6, 29.3, 25.7, 22.7, 22.4, 14.1 **FTIR** (neat): 3315, 2921, 2859, 2367, 2331, 1842, 1739, 1647, 1563, 1534, 1456, 1375, 1261, 1230, 1216, 1072, 1018, 887, 867, 846, 804, 758, 750, 721, 703, 669, 655 cm^{-1}. **HPLC**: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product, (Chiralcel OD-H-OD-H column, hexanes:*i*-PrOH = 99.5:0.5, 1 mL/min, 254 nm), t_{major} = 35.8 min t_{minor} = 41.9 min,; ee = 95%.

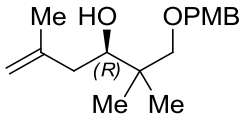
(R)-1-(benzyloxy)-5-methylhex-5-en-3-ol (4.32)



To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), alcohol **4.32a** (33.2 mg, 0.20 mmol, 100 mol%) and β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^oC and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the desired product **4.32** (30.4 mg, 0.138 mmol) as a colorless oil in 69% yield.

TLC (SiO_2): R_f = 0.35 (ethyl acetate: hexanes, 1:4). **[α]$_D^{25}$** = -2.0 (c = 1, CH_2Cl_2), literature value -3.39^o (c = 0.5, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.85-4.84 (m, 1H), 4.78-4.77 (m, 1H), 4.53 (s, 2H), 4.01-3.94 (m, 1H), 3.75-3.70 (m, 1H), 3.68-3.63 (m, 1H) 2.73 (d, *J* = 2.5 Hz, OH), 2.24-2.14 (m, 2H), 1.82-1.70 (m, 2H), 1.75 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 142.7, 138.0, 128.4, 127.7, 127.6, 113.1, 73.3, 68.7, 68.2, 46.0, 36.2, 22.5. **FTIR** (neat): 3441, 3066, 3025, 2920, 2859, 2347, 2335, 1722, 1495, 1453, 1365, 1275, 1205, 1166, 1028, 891, 736, 697, 668 cm^{-1}. **HPLC**: (Chiralcel AS-H column, hexanes:*i*-PrOH = 95:05, 0.5 mL/min, 254 nm), t_{minor} = 8.7 min, t_{major} = 9.5 min; ee = 96%.

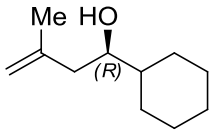
(R)-1-(4-methoxybenzyloxy)-2,2,5-trimethylhex-5-en-3-ol (4.35)



To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), alcohol **4.35a** (44.9 mg, 0.20 mmol, 100 mol%) and β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the desired product **4.35** (50.1 mg, 0.180 mmol) as a colorless oil in 90% yield.

TLC (SiO_2): R_f = 0.31 (ethyl acetate: hexanes, 1:10). **[α]$_D^{25}$** = +2.0 (c = 1, CH_2Cl_2). **^{1}H NMR** (400 MHz, CDCl3): δ 7.25-7.22 (m, 2H), 6.89-6.85 (m, 2H), 4.86-4.84 (m, 1H), 4.80-4.78 (m, 1H), 4.44 (s, 2H), 2.94 (s, 3H), 3.64-3.60 (m, 1H), 3.35 (d, J = 8.86, 1H), 3.27 (d, J = 8.86, 1H), 3.47 (d, J = 3.47, 1H), 2.17 (d, J = 13.7 Hz, 1H), 2.03 (ddd, J = 13.72, 10.66, 0.47 Hz, 1H), 1.77 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (100 MHz, CDCl3): δ 159.1, 143.8, 130.2, 129.1, 113.7, 112.6, 78.9, 74.9, 73.2, 55.3, 40.3, 38.3, 22.5, 22.3, 19.7. **FTIR** (neat): 3484, 3068, 2958, 2933, 2914, 2857, 1646, 1612, 1586, 1513, 1465, 1439, 1362, 1301, 1247, 1207, 1173, 1088, 1036, 889, 820, 756 cm^{-1}. **HRMS** (ESI) Calcd. for $C_{17}H_{26}O_3Na$ $[M+Na]^+$: 301.17742, Found: 301.1773. **HPLC**: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 220 nm), t_{minor} = 13.2 min, t_{major} = 13.8 min; ee = 94%.

(R)-1-cyclohexyl-3-methylbut-3-en-1-ol (4.30)

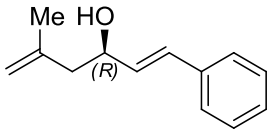


To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was

sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), alcohol **4.30a** (22.8 mg, 0.20 mmol, 100 mol%) and β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 to 1:10) provided the desired product **4.30** (24.3 mg, 0.144 mmol) as a colorless oil in 72% yield.

TLC (SiO_2): R_f = 0.45 (ethyl acetate: hexanes, 1:10). **[α]$_D^{25}$** = -5.0^{o} (c = 1, CH_2Cl_2), literature value for *ent* **3d**, +2.0 (c = 1.4, CCl_4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.90-4.88 (m, 1H), 4.81-4.80 (m, 1H), 3.50-3.45 (m, 1H), 2.24 (ddd, *J* = 13.6, 20.0, 0.4 Hz, 1H) 2.06 (ddd, *J* = 13.6, 10, 0.4 Hz, 1H), 1.89-1.84 (m, 1H), 1.80-1.73 (m, 2H), 1.76 (dd, *J* = 0.4, 0.4 Hz, 3H), 1.71-1.64 (m, 3H), 1.40-1.30 (m, 1H), 1.28-0.99 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 143.3, 113.5, 72.4, 43.4, 43.0, 29.0, 28.2, 26.6, 26.3, 26.2, 22.2. **FTIR** (neat): 3422, 3074, 2978, 2852, 1644, 1449, 1396, 1374, 1259, 1173, 1142, 1100, 1086, 1060, 1044, 986, 953, 864, 842 cm^{-1}. **HPLC**: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product, (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:01, 0.5 mL/min, 254 nm), t_{major} = 9.1 min, t_{minor} = 10.1 min; ee = 92%.

(R,E)-5-methyl-1-phenylhexa-1,5-dien-3-ol (4.33)

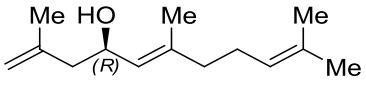


To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), alcohol **4.33a** (26.8 mg, 0.20 mmol, 100 mol%), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%), and isopropanol (31 μL, 0.40 mmol, 200 mol %) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:12 to 1:7) provided the oxidized product (4.5

mg, 0.024 mmol) as a colorless oil in 12% yield and the desired product **4.33** (30.1 mg, 0.160 mmol) as a colorless oil in 80% yield.

TLC (SiO_2): R_f = 0.31 (ethyl acetate: hexanes, 1:4). **[α]$_D^{25}$** = +24.0 (c = 1, CH_2Cl_2), literature value +19.0 (c = 1.44, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.4-7.22 (m, 5H), 6.64 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.24 (dd, *J* = 15.9, 6.3 Hz, 1H), 4.94-4.86 (m, 2H), 4.47-4.42 (m, 1H), 2.39-2.29 (m, 2H), 1.87 (bs, 1H), 1.81 (t, *J* = 1.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 142.0, 136.7, 131.7, 130.1, 128.5, 127.6, 126.4, 114.1, 69.9, 46.2, 22.5. **FTIR** (neat): 3371, 3076, 3026, 2931, 1647, 1599, 1494, 1448, 1274, 1099, 1070, 1046, 965, 891, 747, 740 cm^{-1}. **HPLC**: (Chiralcel OD-H column, hexanes:*i*-PrOH = 90:10, 1 mL/min, 254 nm), t_{major} = 7.1 min, t_{minor} = 12.0 min; ee = 94%.

(R,E)-2,6,10-trimethylundeca-1,5,9-trien-4-ol (4.36)

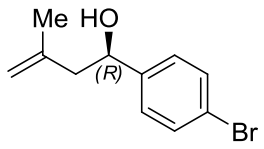


To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), alcohol **4.36a** (30.9 mg, 0.20 mmol, 100 mol%), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%), and isopropanol (31 μL, 0.40 mmol, 200 mol %) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^oC and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:40 to 1:20) provided the desired product **4.36** (33.3 mg, 0.160 mmol) as a colorless oil in 80% yield.

TLC (SiO_2): R_f = 0.40 (ethyl acetate: hexanes, 1:10). **[α]$_D^{25}$** = +13.0 (c = 1, CH_2Cl_2), literature value +19.2 (c = 6.5, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.19 (dq, *J* = 8.4, 1.3 Hz, 1H), 5.11-5.06 (m, 1H), 4.88-4.80 (m, 2H), 4.51 (dt, *J* = 8.5, 4.8 Hz, 1H), 4.45 (ddd, *J* = 13.7, 8.6, 0.9, 1H), 2.19-2.14 (m, 1H), 2.13-1.99 (m, 4H), 1.78 (t, *J* = 0.9, 3H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.68 (d, *J* = 1.1 Hz, 3H), 1.60 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 142.4, 138.6, 131.6, 127.1, 123.9, 66.0, 46.2, 39.5, 26.3, 25.7, 22.5, 17.7, 16.6. **FTIR** (neat): 3362, 3074, 2967, 2916, 2855,

2322, 1647, 1442, 1375, 1261, 1201, 1139, 1105, 1046, 1008, 979, 887 cm^{-1}. **HPLC**: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product, (Chiralcel OJ-H/AS-H column, hexanes:*i*-PrOH = 99:1, 0.4 mL/min, 254 nm), t_{major} = 22.6 min, t_{minor} = 24.2 min; ee = 94%.

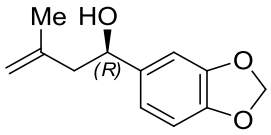
(R)-1-(4-bromophenyl)-3-methylbut-3-en-1-ol (4.34)



To a resealable pressure tube equipped with a magnetic stir bar was added alcohol **4.34a** (37.4 mg, 0.20 mmol, 100 mol%), ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M) and β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the oxidized product (6.7 mg, 0.028 mmol) as white solid in 14% yield and the desired product **4.34** (40.0 mg, 0.166 mmol) as white solid in 83% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate: hexanes, 1:5). **m.p.**: 72-73 ^{o}C. **[α]$_D^{25}$** = +45.0^{o} (c = 1, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz 2H), 4.94-4.93 (m, 1H), 4.85-4.84 (m, 1H), 4.78-4.75 (m, 1H), 2.39-2.36 (m, 2H), 2.18 (d, *J* = 2.4 Hz, 1H), 1.79 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 143.0, 142.0, 131.5, 127.5, 121.2, 114.5, 70.7, 48.4, 22.3. **FTIR** (neat): 3358, 3075, 2976, 2934, 1900, 1803, 1648, 1592, 1488, 1472, 1406, 1373, 1336, 1304, 1202, 1169, 1046, 1008, 902, 874, 822, 803, 718 cm^{-1}. **HPLC**: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:05, 1 mL/min, 254 nm), t_{minor} = 8.7 min, t_{major} = 9.5 min; ee = 96%.

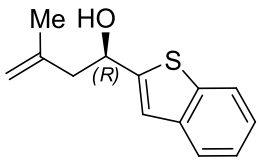
(R)-1-(benzo[d][1,3]dioxol-5-yl)-3-methylbut-3-en-1-ol (4.31)



To a resealable pressure tube equipped with a magnetic stir bar was added alcohol **4.31a** (30.4 mg, 0.20 mmol, 100 mol%), ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M) and β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 to 1:10) provided the oxidized product (2.0 mg, 0.010 mmol) as a colorless oil in 5% yield and the desired product **4.31** (32.2 mg, 0.156 mmol) as a colorless oil in 78% yield.

TLC (SiO_2): R_f = 0.28 (ethyl acetate: hexanes, 1:4). **[α]$_D^{25}$** = +50.0 (c = 1, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.90 (dt, *J* = 1.69, 0.44 Hz, 1H), 6.82 (ddd, *J* = 8.0, 1.7, 0.57 Hz, 1H), 6.77 (dd, *J* = 8.0, 0.32 Hz, 1H), 5.95 (s, 2H), 4.93-4.83 (m, 2H), 4.73 (dd, *J* = 8.4, 5.1, 1H), 2.44-2.34 (m, 2H), 2.07 (bs, 1H), 1.79 (t, *J* = 1.0, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 147.7, 146.8, 142.3, 138.1, 119.1, 114.1, 108.0, 106.3, 101.0, 71.2, 48.3, 22.3. **FTIR** (neat): 3408, 3076, 2897, 1726, 1646, 1609, 1503, 1487, 1442, 1376, 1187, 1124, 1094, 1209, 1186, 1124, 1094, 1010, 932, 896, 810, 783, 750, 727 cm^{-1}. **HPLC**: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 280 nm), t_{minor} = 15.3 min, t_{major} = 16.6 min; ee = 94%.

(R)-1-(benzo[b]thiophen-2-yl)-3-methylbut-3-en-1-ol (4.37)



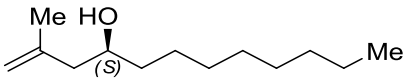
To a resealable pressure tube equipped with a magnetic stir bar was added alcohol **4.37a** (32.8 mg, 0.20 mmol, 100 mol%), ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate

(42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M) and β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 to 1:10) provided the oxidized product (2.2 mg, 0.010 mmol) as a white solid in 5% yield and the desired product **4.37** (38.0 mg, 0.174 mmol) as a white solid in 87% yield.

TLC (SiO_2): R_f = 0.25 (ethyl acetate: hexanes, 1:4). **m.p.**: 78-80 ^{o}C. **[α]$_D^{25}$** = +36.1 (c = 1, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83-7.81 (m, 1H), 7.73-7.71 (m, 1H), 7.36-7.28 (m, 2H), 7.22 (t, *J* = 0.74, 1H), 5.16 (t, *J* = 6.76, 1H), 4.97-4.90 (m, 2H), 2.65-2.57 (m, 2H), 2.32 (bs, 1H), 1.12 (t, *J* = 1.1 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 148.6, 141.5, 139.5, 139.2, 124.2, 124.1, 123.4, 122.4, 120.0, 114.7, 68.1, 47.9, 22.4. **FTIR** (neat): 3556, 3069, 2966, 2937, 1643, 1457, 1438, 1376, 1326, 1275, 1261, 1155, 1118, 1054, 973, 946, 899, 876, 845, 831, 754, 728, 669 cm^{-1}. **HRMS** (CI) Calcd. for $C_{13}H_{14}OS$ $[M]^+$: 218.0766, Found: 218.0765. **HPLC**: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 254 nm), t_{minor} = 19.8 min, t_{major} = 26.0 min; ee = 96%.

4.4.3 Experiment details of Methallylation from Aldehyde Oxidation Level

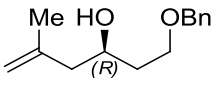
(S)-2-methyldodec-1-en-4-ol (4.29)



To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), aldehyde **4.29b** (28.4 mg, 0.20 mmol, 100 mol%), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%), and isopropanol (31 μL, 0.40 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:40 to 1:20) provided the desired product **4.29** (29.8 mg, 0.150 mmol) as a colorless oil in 75% yield.

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product, (Chiralcel OD-H-OD-H column, hexanes:*i*-PrOH = 99.5:0.5, 1 mL/min, 254 nm), t_{major} = 36.2 min t_{minor} = 42.3 min,; ee = 97%.

(R)-1-(benzyloxy)-5-methylhex-5-en-3-ol (4.32)

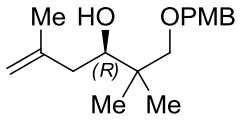


To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), aldehyde **4.32b** (32.8 mg, 0.20 mmol, 100 mol%), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%) and isopropanol (31 μL, 0.40 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column

chromatography (SiO_2; ethyl acetate: hexanes, 1:9 to 1:5) provided the desired product **4.32** (24.2 mg, 0.110 mmol) as a colorless oil in 55% yield.

HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 95:05, 0.5 mL/min, 254 nm), t_{minor} = 10.0 min, t_{major} = 11.0 min; ee = 97%.

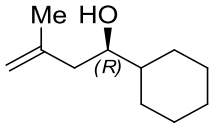
(R)-1-(4-methoxybenzyloxy)-2,2,5-trimethylhex-5-en-3-ol (4.35)



To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), aldehyde **4.35b** (44.5 mg, 0.20 mmol, 100 mol%), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%), and isopropanol (31 μL, 0.40 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the desired product **4.35** (50.7 mg, 0.182 mmol) as a colorless oil in 91% yield.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 220 nm), t_{minor} = 12.0 min, t_{major} = 12.6 min; ee = 97%.

(R)-1-cyclohexyl-3-methylbut-3-en-1-ol (4.30)

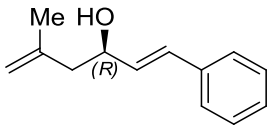


To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), aldehyde **4.30b** (22.4 mg, 0.20 mmol, 100 mol%), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%) and

isopropanol (31 μL, 0.40 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20) provided the desired product **4.30** (24.9 mg, 0.148 mmol) as a colorless oil in 74% yield.

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product, (Chiralcel AS-H column, hexanes:*i*-PrOH = 99:01, 0.5 mL/min, 254 nm), t_{major} = 8.9 min, t_{minor} = 9.7 min; ee = 91%.

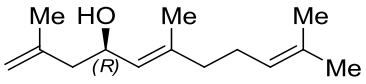
(R,E)-5-methyl-1-phenylhexa-1,5-dien-3-ol (4.33)



To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), aldehyde **4.33b** (26.4 mg, 0.20 mmol, 100 mol%), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%), and isopropanol (62 μL, 0.80 mmol, 400 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:12 to 1:7) provided the oxidized product **4e** (4.8 mg, 0.026 mmol) as a colorless oil in 13% yield and the desired product **4.33** (30.9 mg, 0.164 mmol) as a colorless oil in 82% yield.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 90:10, 1 mL/min, 254 nm), t_{major} = 7.1 min, t_{minor} = 12.0 min; ee = 95%.

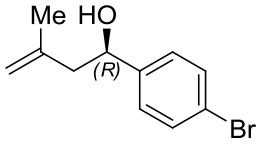
(R,E)-2,6,10-trimethylundeca-1,5,9-trien-4-ol (4.36)



To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), aldehyde **4.36b** (30.4 mg, 0.20 mmol, 100 mol%), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%), and isopropanol (62 μL, 0.80 mmol, 400 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:40 to 1:20) provided the oxidized product (2.5 mg, 0.012 mmol) as a colorless oil in 6% yield and the desired product **4.36** (31.3 mg, 0.150 mmol) as a colorless oil in 75% yield.

HPLC: Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product, (Chiralcel OJ-H/AS-H column, hexanes:*i*-PrOH = 99:1, 0.4 mL/min, 254 nm), t_{major} = 25.0 min, t_{minor} = 27.0 min; ee = 93%.

(R)-1-(4-bromophenyl)-3-methylbut-3-en-1-ol (4.34)

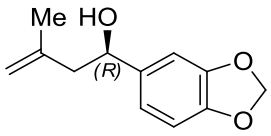


To a resealable pressure tube equipped with a magnetic stir bar was added aldehyde **4.34b** (37.0 mg, 0.20 mmol, 100 mol%), ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%) and isopropanol (31 μL, 0.40 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column

chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the oxidized product (3.8 mg, 0.016 mmol) as white solid in 14% yield and the desired product **4.34** (43.5 mg, 0.180 mmol) as white solid in 83% yield.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:05, 1 mL/min, 254 nm), t_{minor} = 8.7 min, t_{major} = 9.5 min; ee = 95%.

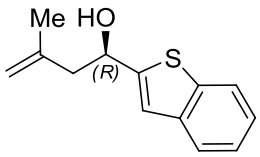
(R)-1-(benzo[d][1,3]dioxol-5-yl)-3-methylbut-3-en-1-ol (4.31)



To a resealable pressure tube equipped with a magnetic stir bar was added aldehyde **4.31b** (30.0 mg, 0.20 mmol, 100 mol%), ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%), and isopropanol (31 μL, 0.40 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 to 1:10) provided the oxidized product (4.0 mg, 0.020 mmol) as a colorless oil in 10% yield and the desired product **4.31** (35.1 mg, 0.170 mmol) as a colorless oil in 85% yield.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 280 nm), t_{minor} = 14.3 min, t_{major} = 15.6 min; ee = 96%.

(R)-1-(benzo[b]thiophen-2-yl)-3-methylbut-3-en-1-ol (4.37)

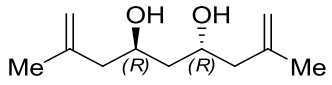


To a resealable pressure tube equipped with a magnetic stir bar was added aldehyde **4.37b** (32.4 mg, 0.20 mmol, 100 mol%), ***(R)*-II** (10.7 mg, 0.01 mmol, 5 mol%) and dry potassium phosphate (42.4 mg, 0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.2 mL, 1.0 M), β-methallyl chloride (54.3 mg, 0.60 mmol, 300 mol%), and isopropanol (31 μL, 0.40 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 to 1:10) provided the oxidized product (2.2 mg, 0.010 mmol) as white solid in 5% yield and the desired product **4.37** (39.7 mg, 0.182 mmol) as a white solid in 91% yield.

HPLC: (Chiralcel OJ-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 254 nm), t_{minor} = 19.8 min, t_{major} = 26.3 min; ee = 96%.

4.4.4 Experiment details of Bis-methallylation of Propanediol

(4R,6R)-2,8-dimethylnona-1,8-diene-4,6-diol (4.39)

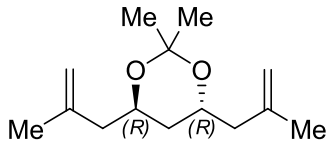


To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-II** (32.2 mg, 0.03 mmol, 10 mol%) and dry potassium phosphate (127.4 mg, 0.60 mmol, 200 mol%). The tube was sealed with a rubber septum and purged with nitrogen. THF (0.6 mL, 0.5 M), alcohol **4.28** (22.8 mg, 0.30 mmol, 100 mol%) and β-methallyl chloride (135.8 mg, 1.50 mmol, 500 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 50 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:5 to 1:3) provided the desired product **4.38** (36.5 mg, 0.198 mmol) as a white solid in 66% yield.

TLC (SiO_2): R_f = 0.20 (ethyl acetate: hexanes, 1:4). **m.p.**: 75-76 ^{o}C. **[α]$_D^{25}$** = -24.0^{o} (c = 1, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.89-4.87 (m, 2H), 4.80-4.79 (m, 2H), 4.14-4.07 (m, 2H), 2.52 (s, 2H), 2.27-2.16 (m, 4H), 1.77 (s, 6H), 1.62 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR** (100 MHz,

$CDCl_3$): δ 142.5, 113.5, 66.0, 46.1, 42.3, 22.4. **FTIR** (neat): 3370, 3293, 3075, 2968, 2939, 1778, 1651, 1438, 1397, 1371, 1325, 1292, 1244, 1212, 1183, 1100, 1062, 1038, 989, 974 cm^{-1}. **HRMS** (ESI) Calcd. for $C_{11}H_{20}O_2Na$ $[M+Na]^+$: 207.13555, Found: 207.1356. **HPLC**: Enantiomeric excess was determined by HPLC analysis of the bis-4-nitrobenzoate derivative of the product, (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:05, 1 mL/min, 254 nm), t_{minor} = 12.7 min, t_{meso} = 12.8 and t_{major} = 20.7 min; ee = 99%.

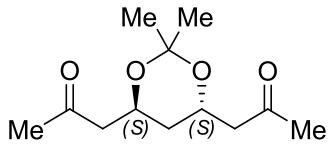
(4R,6R)-2,2-dimethyl-4,6-bis(2-methylallyl)-1,3-dioxane (4.40)



To a stirred solution of diol **6** (33 mg, 0.179 mmol, 100 mol%) in dichloromethane (1.8 mL, 0.1 M) was added 2,2-dimethoxypropane (278 mg, 2.685 mmol, 1500 mol%) and pyridinium p-toluenesulfonate (4.5 mg, 0.018 mmol, 10 mol%). The reaction mixture was stirred for 2 hr at ambient temperature at which TLC comparison show complete conversion. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (4 mL) and extracted with dichloromethane (5 mL x 3). The combined organic extracts were dried with (MgSO4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO2: ethyl acetate:hexanes, 1:20 with 0.1% TEA) to give the acetonide **4.40** (30.4 g, 0.135 mmol) as a colorless oil in 76% yield.

TLC (SiO_2): R_f = 0.50 (ethyl acetate: hexanes, 1:20). **[α]$_D^{25}$** = -28.0^o (c = 1, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.79-4.78 (m, 2H), 4.75-4.74 (m, 2H), 4.03-3.96 (m, 2H), 2.31-2.25 (m, 2H), 2.15-2.10 (m, 2H), 1.74 (s, 6H), 1.60 (t, 2H), 1.37 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 142.3, 112.1, 100.3, 65.0, 44.0, 38.1, 24.8, 22.8. **FTIR** (neat): 3075, 2986, 2937, 1650, 1443, 1376, 1230, 1166, 1114, 1025, 987, 939, 821 cm^{-1}. **HRMS** (CI) Calcd. for $C_{14}H_{24}O_2$ $[M]^+$: 225.1855, Found: 225.1856.

1,1'-((4S,6S)-2,2-dimethyl-1,3-dioxane-4,6-diyl)dipropan-2-one (4.41)



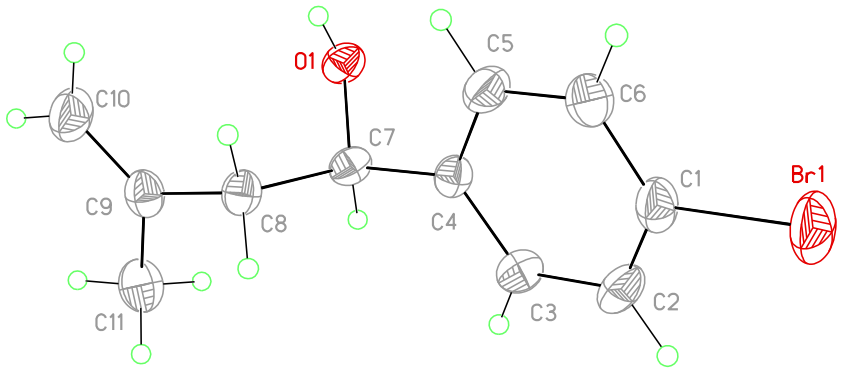
To a stirred solution of acetonide 7 (39 mg, 0.174 mmol, 100 mol%) in dichloromethane (3.5 mL, 0.05 M) was bubbled ozone at -78 ^{o}C for around 5 min till a blue color persisted. O_2 was bubbled for 2 min followed by argon for 10 min. Triphenylphosphine (183 mg, 0.696 mmol, 400 mol%) was added and the reaction mixture was slowly warmed to ambient temperature overnight. The reaction mixture was concentrated in vacuo and residue was purified by column chromatography (SiO2: ethyl acetate:hexanes, 1:2 with 0.1% TEA) to give the diketone **4.41** (26.0 mg, 0.114 mmol) as a colorless oil in 65% yield.

TLC (SiO_2): R_f = 0.35 (ethyl acetate: hexanes, 1:2). **[α]$_D^{25}$** = -37.0^{o} (c = 1, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.27 (ddd, , *J* = 15.6, 7.6, 4.8 Hz, 2H), 2.75-2.69 (m, 2H), 2.50-2.45 (m, 2H), 2.17 (s, 6H), 1.68 (t, , *J* = 7.6 Hz, 2H), 1.33 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.6, 100.7, 62.8, 49.4, 37.7, 30.8, 24.5. **FTIR** (neat): 3753, 3504, 2988, 2937, 2854, 2370, 2331, 1698, 1423, 1380, 1367, 1306, 1223, 1170, 1121, 1092, 1032, 1011, 930 cm^{-1}. **HRMS** (ESI) Calcd. for $C_{12}H_{20}O_4Na$ $[M+Na]^+$: 251.1254, Found: 251.1254.

4.4.5. Absolute Stereochemical determination

The absolute stereochemistry was determined by single crystal x-ray analysis of product **4.34** and was found to be ***R***, see figure 4.1.

Figure 4.1. View of **4.34** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



4.4.6 Part Two: 1,2-Disubstituted Olefins as Allyl Donors in Iridium Catalyzed Transfer Hydrogenation Transformation. Enantioselective Vinylogous Aldol-Reformatsky Addition

Synthesis of Catalyst of (*R*)-I and (*S*)-I

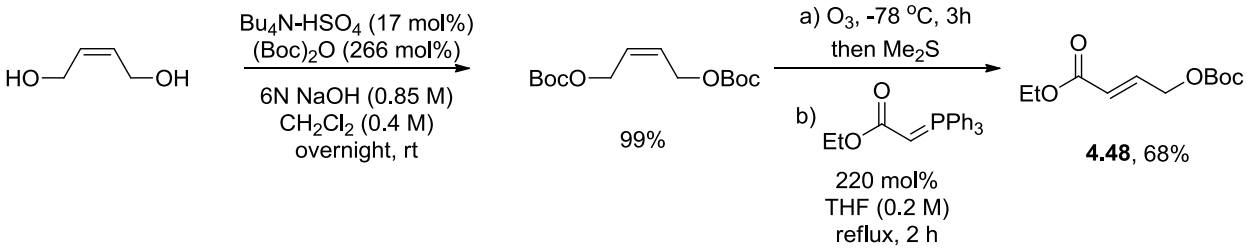
Preparation of (*R*)-I

To a mixture of $[Ir(cod)Cl]_2$ (134.3 mg, 0.20 mmol, 100 mol%), (*R*)-Cl,MeO-BIPHEP (260.6 mg, 0.40 mmol, 200 mol%), Cs_2CO_3 (260.6 mg, 0.80 mmol, 400 mol%), 4-Cl-3-NO_2BzOH (161.2 mg, 0.89 mmol, 400 mol%) and allyl acetate (100.1 mg, 1.0 mmol, 500 mol%) in a sealed tube under N_2 atmosphere was added THF (4.0 mL, 0.05 M). The reaction mixture was allowed to stir for 30 min at ambient temperature and was then heated at 80 ^oC for 1.5 hr, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered and washed with THF (10 mL). The filtrate was concentrated *in vacuo* and desolved in THF (2 mL) and hexane (50 mL) was added. A yellow precipitate formed which was sonicated for 5 minutes, collected by filtration and dried under vacuum to provide (*R*)-I (342.0 mg, 0.316 mmol) in 79% yield.

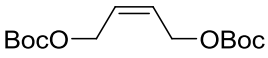
Preparation of (*S*)-I

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*S*)-Cl,MeO-BIPHEP (169.4 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-Cl-3-NO_2BzOH (104.8 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under an atmosphere of N_2 was added THF (2.6 mL, 0.05 M). The reaction mixture was allowed to stir for 30 min at ambient temperature and was then heated at 80 ^oC for 1.5 hr, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered and washed with THF (8 mL). The filtrate was concentrated *in vacuo* and desolved in THF (2 mL) and hexane (40 mL) was added. A yellow precipitate formed which was sonicated for 5 minutes, collected by filtration and dried under vacuum to provide (*S*)-**I** (228.3 mg, 0.211 mmol) in 81% yield.

Synthesis of starting material 4.48



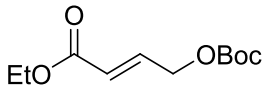
(*Z*)-but-2-ene-1,4-diyl tert-butyl dicarbonate



A 500 mL round bottom flask was charged with *cis*-2-butenediol (5.27 g, 60 mmol, 100 mol%), tetrabutylammonium hydrogen sulfate (3.46 g, 10.2 mmol, 17 mol%) and the mixture was dissolved in 6N NaOH (70 mL, 0.85 M) and CH_2Cl_2 (150 mL, 0.4 M). Boc-Anhydride (34.83 g, 159.6 mmol, 266 mol%) was added as a solid and the reaction mixture was allowed to stir at ambient temperature overnight. The reaction mixture was transferred to seperatory funnel, diluted with CH_2Cl_2 and washed with water (3 x 300 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to give the title compound (17.13 g, 59.40 mmol) in 99% yield as colorless oil and was used without further purification.

TLC (SiO_2): R_f = 0.60 (ethyl acetate: hexanes, 1:9). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.80-5.78 (m, 2H), 4.68-4.66 (m, 4H), 1.49 (s, 18H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.2, 128.0, 82.4, 62.2, 27.9. **FTIR** (neat): 2981, 2928, 1739, 1458, 1394, 1369, 1347, 1270, 1250, 1156, 1089, 966, 929, 859, 792 cm^{-1}. **HRMS** (CI) Calcd. for $C_{14}H_{25}O_6$ $[M+H]^+$: 289.1651, Found: 289.1655.

(*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate (4.48)



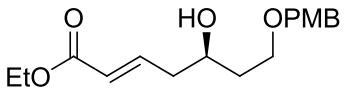
To (*Z*)-but-2-ene-1,4-diyl tert-butyl dicarbonate (10 g, 34.68 mmol, 100 mol%) was added CH_2Cl_2 (115 mL, 0.3 M) and the temperature was lowered to -78 ^oC. Ozone was passed through the solution (~ 3h) until a deep blue color persisted, at which point TLC analysis revealed complete consumption of starting material. Argon was passed through solution for 30 min and dimethyl sulfide (21.56 g, 347.03 mmol, 1000 mol%) was added at -78 ^oC. The cooling bath was removed and the reaction mixture was allowed to stir overnight. The reaction mixture was concentrated *in vacuo* to give crude aldehyde, which was used immediately without further purification.

To the aldehyde in a 500 mL round bottom flask was added THF (180 mL, 0.2M) and Ethyl (triphenylphosphoranylidene)acetate (26.58 g, 76.29 mmol, 220 mol%). The reaction vessel was equipped with a reflux condenser and the reaction mixture was heated to reflux for 2 h. The reaction mixture was allowed to cool to ambient temperature and was concentrated *in vacuo*, diluted with hexane (180 mL), which resulted in precipitation and the suspension was filtered through a pad of celite. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (SiO_2; ethyl acetate: hexanes, 0:100 to 5:95) to furnish the title compound (10.86 g, 47.16 mmol) as a colorless oil in 68% yield over two steps.

TLC (SiO_2): R_f = 0.45 (ethyl acetate: hexanes, 1:4). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.94 (dt, *J* = 15.6, 4.8 Hz, 1H), 6.06 (dt, *J* = 15.6, 2 Hz, 1H), 4.73 (dd, *J* = 4.4, 2.0 Hz, 2H), 2.09 (q, *J* = 7.2 Hz, 2H), 1.50 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.8, 152.9, 140.9, 122.3, 82.7, 64.9, 60.6, 27.7, 14.2. **FTIR** (neat): 2981, 2936, 2905, 1743, 1721, 1667, 1457, 1394, 1369, 1275, 1251, 1157, 1120, 1094, 1037, 968, 934, 851, 792, 769 cm^{-1}. **HRMS** (CI) Calcd. for $C_{11}H_{19}O_5$ $[M+H]^+$: 231.1233, Found: 231.1233.

4.4.7 Experiment details and Spectral Data of Reaction from Alcohol Oxidation Level

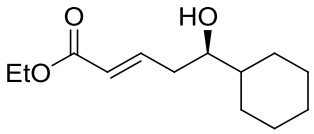
(*R*)-(*E*)-ethyl 5-hydroxy-7-(4-methoxybenzyloxy)hept-2-enoate (4.69)



To a resealable pressure tube equipped with a magnetic stir bar was added ***(R)*-I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), alcohol **4.69a** (58.9 mg, 0.30 mmol, 100 mol%) and (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:4 to 1:2) provided the branched product (55.5 mg, 0.180 mmol, 1:1 dr) as a colorless oil in 60% yield, and the desired linear product **4.69** (24.6 mg, 0.080 mmol) as a colorless oil in 27% yield.

TLC (SiO_2): R_f = 0.25 (ethyl acetate: hexanes, 1:2). **[α]$_D^{25}$** = +13.0 (c = 1, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (dt, *J* = 8.8, 2.8 Hz, 2H), 6.97 (dt, *J* = 15.6, 7.2 Hz, 1H), 6.88 (dt, *J* = 8.8, 2.8 Hz, 2H), 5.88 (dt, 15.6, 1.2 Hz, 1H), 4.45 (s, 2H), 4.18 (q, *J* = 7.2, 2H), 3.98-3.95 (m, 1H), 3.81 (s, 3H), 3.73-3.70 (m, 1H), 3.65-3.59 (m, 1H), 3.16 (d, *J* = 2.8 Hz, 1H), 2.40-2.34 (m, 2H), 1.79-1.73 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.3, 159.3, 145.1, 129.7, 129.4, 123.6, 113.9, 73.0, 70.4, 68.7, 60.2, 55.3, 40.1, 35.8, 14.2. **FTIR** (neat): 3484, 3453, 3431, 2976, 2935, 2861, 1714, 1654, 1612, 1586, 1513, 1464, 1367, 1302, 1246, 1204, 1171, 1091, 1034, 980, 820, 756, 708 cm^{-1}. **HRMS** (CI) Calcd. for $C_{17}H_{24}O_5$ $[M]^+$: 308.1624, Found: 308.1613. **HPLC**: (Chiralcel AS-H column, hexanes:*i*-PrOH = 90:10, 1 mL/min, 254 nm), t_{minor} = 10.8 min, t_{major} = 12.3 min; ee = 88%.

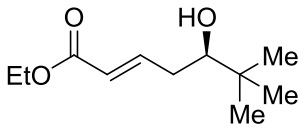
(*R*)-(*E*)-ethyl 5-cyclohexyl-5-hydroxypent-2-enoate (4.60)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), alcohol **4.60a** (34.2 mg, 0.30 mmol, 100 mol%) and (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the branched product (9.5 mg, 0.042 mmol, 1:1 dr) as a colorless oil in 14% yield, and the desired linear product **4.60** (42.5 mg, 0.188 mmol) as a colorless oil in 63% yield.

TLC (SiO_2): R_f = 0.25 (ethyl acetate: hexanes, 1:4). **[α]$_D^{25}$** = -11.0 (c = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.01 (ddd, *J* = 15.6, 7.6, 6.8 Hz, 1H), 5.91 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.51 (dt, *J* = 14, 4.8 Hz, 1H), 2.46-2.28 (m, 2H), 1.87-1.74 (m, 4H), 1.73-1.65 (m, 2H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.41-0.97 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.4, 146.0, 123.5, 74.6, 60.2, 43.2, 37.1, 29.0, 27.8, 26.3, 26.1, 25.9, 14.2 Hz. **FTIR** (neat): 3434, 2972, 2851, 1718, 1702, 1652, 1449, 1393, 1368, 1318, 1265, 1206, 1162, 1695, 1039, 977, 892, 828, 712 cm^{-1}. **HRMS** (CI) Calcd. for $C_{13}H_{23}O_3$ $[M+H]^+$: 227.1647, Found: 227.1646. **HPLC**: (Chiralcel AD-H column, hexanes:*i*-PrOH = 90:10, 0.5 mL/min, 254 nm), t_{major} = 14.2 min, t_{minor} = 14.9 min; ee = 95%.

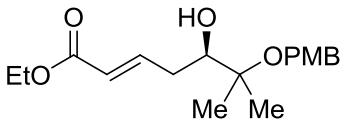
(*R*)-(*E*)-ethyl 5-hydroxy-6,6-dimethylhept-2-enoate (4.62)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%) and alcohol **4.62a** (26.5 mg, 0.30 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M) and (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 to 1:10) provided the desired linear product **4.62** (35.5 mg, 0.177 mmol) as a colorless oil in 59% yield.

TLC (SiO_2): R_f = 0.20 (ethyl acetate: hexanes, 1:6). **[α]$_D^{25}$** = +37.0 (c = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.04 (ddd, *J* = 15.6, 8, 6.4 Hz, 1H), 5.92 (dt, , *J* = 15.6, 1.2 Hz, 1H), 4.19 (q, , *J* = 6.8 Hz, 2H), 3.39-3.35 (m, 1H), 2.48-2.41 (m, 1H), 2.23-2.14 (m, 1H), 1.67 (br s, 1H), 1.29 (t, , *J* = 6.8 Hz, 3H), 0.93 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.4, 147.1, 123.4, 78.3, 60.2, 35.0, 34.8, 25.6, 14.2. **FTIR** (neat): 3471, 2956, 2871, 1702, 1652, 1478, 1393, 1366, 1267, 1245, 1158, 1095, 1067, 1041, 1009, 976, 934, 914, 771, 704 cm^{-1}. **HRMS** (CI) Calcd. for $C_{11}H_{21}O_3$ $[M+H]^+$: 201.1491, Found: 201.1491. **HPLC**: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 11.4 min, t_{major} = 12.3 min; ee = 96%.

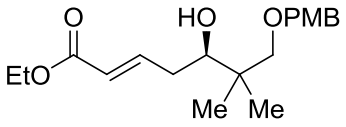
(*R*)-(*E*)-ethyl 5-hydroxy-6-(4-methoxybenzyloxy)-6-methylhept-2-enoate (4.68)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), alcohol **4.68a** (62.8 mg, 0.30 mmol, 100 mol%) and (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 0:1 to 3:7) provided the desired linear product **4.68** (85.0 mg, 0.264 mmol) as a colorless oil in 88% yield.

TLC (SiO_2): R_f = 0.33 (ethyl acetate: hexanes, 3:7). **[α]$_D^{25}$** = +18 (c = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): 7.23 (d, *J* = 8.8 Hz, 2H), 7.07 (dt, *J* = 15.6, 1.2 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.92 (dt, *J* = 15.6, 1.2 Hz, 1H), 4.40 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.67 - 3.63 (m, 1H), 2.54 (d, *J* = 3.2 Hz, 1H), 2.46 – 2.28 (m, 2H), 1.30 – 1.23 (m, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.4, 159.1, 146.6, 131.0, 128.9, 123.1, 113.8, 77.6, 76.0, 63.5, 60.2, 55.3, 34.4, 21.5, 20.1, 14.3. **FTIR** (neat): 3488, 2976, 1714, 1653, 1612, 1586, 1513, 1464, 1386, 1367, 1321, 1300, 1246, 1212, 1170, 1148, 1035, 978, 893, 821, 749, 705 cm^{-1}. **HRMS** (CI) Calcd. for $C_{18}H_{26}O_5$ $[M]^+$: 322.1780, Found: 322.1780. **HPLC**: (Chiralcel OD-H column, hexanes:*i*-PrOH = 96:4, 0.75 mL/min, 210 nm), t_{minor} = 21.6 min; t_{major} = 26.4 min, ee = 96%.

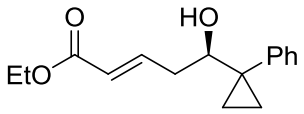
(*R*)-(*E*)-ethyl 5-hydroxy-7-(4-methoxybenzyloxy)-6,6-dimethylhept-2-enoate (4.65)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), alcohol **4.65a** (67.2 mg, 0.30 mmol, 100 mol%) and (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 0:1 to 3:7) provided the desired linear product **4.65** (76.0 mg, 0.226 mmol) as a colorless oil in 75% yield.

TLC (SiO_2): R_f = 0.33 (ethyl acetate: hexanes, 3:7). **[α]$_D^{25}$** = +25 (c = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): 7.23 (d, *J* = 8.4 Hz, 2H), 7.07 (dt, *J* = 16.0, 1.2 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.88 (dt, *J* = 16.0, 1.2 Hz, 1H), 4.43 (d, *J* = 8.4 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.62 – 3.56 (m, 1H), 3.36 (d, *J* = 3.6 Hz, 1H), 3.35 (d, *J* = 9.2 Hz, 1H), 3.27 (d, *J* = 9.2 Hz, 1H), 2.40 – 2.30 (m, 1H), 2.25 – 2.15 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.92 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.4, 159.3, 147.4, 129.7, 129.2, 122.8, 113.8, 79.3, 77.4, 73.3, 60.1, 55.2, 38.3, 35.0, 22.8, 19.6, 14.3. **FTIR** (neat): 3482, 2959, 2872, 1714, 1653, 1612, 1586, 1513, 1465, 1366, 1321, 1301, 1246, 1209, 1172, 1083, 1035, 978, 912, 819, 755, 706 cm^{-1}. **HRMS** (CI) Calcd. for $C_{19}H_{28}O_5$ $[M]^+$: 336.1937, Found: 336.1937. **HPLC**: (Chiralcel OD-H column, hexanes:*i*-PrOH = 96:4, 0.75 mL/min, 280 nm), t_{major} = 23.3 min, t_{minor} = 22.4 min; ee = 99%.

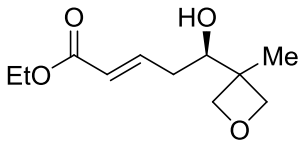
(*R*)-(*E*)-ethyl 5-hydroxy-5-(1-phenylcyclopropyl)pent-2-enoate (4.63)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%) and alcohol **4.63a** (44.5 mg, 0.30 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), and (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the desired linear product **4.63** (54.9.9 mg, 0.211 mmol) as a colorless oil in 70% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate: hexanes, 1:4). $[\alpha]_D^{25}$ = -60.0 (c = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.35 (m, 2H), 7.33-7.29 (m, 2H), 7.27-7.23 (m, 1H), 6.96 (dt, *J* = 15.6, 7.6 Hz, 1H), 5.83 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.31-3.26 (m, 1H), 2.47-2.40 (m, 1H), 2.19-2.11 (m, 1H), 1.73 (d, *J* = 5.6 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.90-0.86 (m, 2H), 0.84-0.80 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.3, 145.7, 140.6, 131.0, 128.2, 127.0, 123.4, 77.3, 60.2, 38.1, 31.3, 14.2, 11.1, 10.2. **FTIR** (neat): 3455, 3079, 3057, 2981, 2901, 1699, 1652, 1601, 1496, 1445, 1426, 1392, 1368, 1315, 1268, 1205, 1040, 977, 936, 762, 701 cm^{-1}. **HRMS** (CI) Calcd. for $C_{16}H_{21}O_3$ $[M+H]^+$: 261.1491, Found: 261.1490. **HPLC**: (Chiralcel AD-H column, hexanes:*i*-PrOH = 90:10, 1 mL/min, 254 nm), t_{major} = 8.6 min, t_{minor} = 10.1 min; ee = 97%.

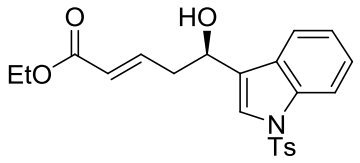
(*R*)-(*E*)-ethyl 5-hydroxy-5-(3-methyloxetan-3-yl)pent-2-enoate (4.66)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), alcohol **4.66a** (30.6 mg, 0.30 mmol, 100 mol%) and (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:3 to 1:1) provided the desired linear product **4.68** (48.2.9 mg, 0.225 mmol) as a colorless oil in 61% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate: hexanes, 1:1). $[\ \alpha\ ]_D^{25}$ = +06.0 (c = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.99 (ddd, *J* = 15.6, 8, 7.2 Hz, 1H), 5.94 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.64 (d, *J* = 6 Hz, 1H), 4.51 (d, *J* = 6 Hz, 1H), 4.35 (d, *J* = 6 Hz, 1H), 4.32 (d, *J* = 6 Hz, 1H), 4.20 (d, *J* = 7.2 Hz, 2H), 4.04 (m, 1H), 2.44 (br s, 1H), 2.33-2.20 (m, 2H), 1.33 (s, 3H), 1.30 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.2, 145.0, 124.1, 80.5, 79.5, 74.2, 60.4, 43.3, 35.0, 18.6, 14.2. **FTIR** (neat): 3419, 2962, 2928, 2873, 1715, 1653, 1456, 1369, 1321, 1265, 1215, 1159, 1040, 975, 827, 699 cm^{-1}. **HRMS** (CI) Calcd. for $C_{11}H_{19}O_4$ $[M+H]^+$: 215.1283, Found: 215.1286. **HPLC**: (Chiralcel OB-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 254 nm), t_{minor} = 10.2 min, t_{major} = 11.6 min; ee = 90%.

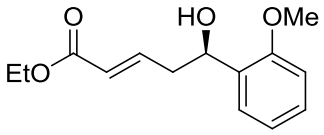
(*R*)-(*E*)-ethyl 5-hydroxy-5-(1-tosyl-1H-indol-3-yl)pent-2-enoate (4.67)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), alcohol **4.67a** (90.4 mg, 0.30 mmol, 100 mol%) and (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the branched product (16.0 mg, 0.039 mmol, 1:1 dr) as a colorless oil in 13% yield and the desired linear product **4.68** (83.3 mg, 0.201 mmol) as a light brown gummy solid in 67% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate: hexanes, 1:4). **[α]$_D^{25}$** = -37.0 (c = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.64 (dt, *J* = 8.4, 2 Hz, 2H), 7.47 (dt *J* = 7.2, 0.8 Hz, 1H), 7.32-7.28 (m, 1H), 7.23 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.18 (app d, *J* = 8.8 Hz, 2H), 7.05 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.68 (t, *J* = 0.8 Hz, 1H), 5.95 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.37-5.33 (m, 1H), 4.18, (q, *J* = 6.8Hz, 2H), 3.34 (d, *J* = 4.8 Hz, 1H), 2.98-2.82 (m, 2H), 2.32 (s 3H), 1.28 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.2, 145.2, 144.4, 142.6, 137.2, 135.4, 129.9, 129.0, 126.2, 125.1, 124.0, 123.9, 121.2, 114.8, 109.6, 65.9, 60.3, 38.4, 21.5, 14.2. **FTIR** (neat): 3449, 3061, 2981, 2926, 1715, 1655, 1596, 1451, 1451, 1367, 1306, 1274, 1213, 1188, 1173, 1149, 1120, 1090, 1044, 978, 813, 750, 704, 675, 655 cm^{-1}. **HRMS** (CI) Calcd. for $C_{22}H_{24}NO_5S$ $[M+H]^+$: 414.1375, Found: 414.1356. **HPLC**: (Chiralcel AS-H column, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 254 nm), t_{major} = 11.1 min, t_{minor} = 16.4 min; ee = 95%.

(*R*)-(*E*)-ethyl 5-hydroxy-5-(2-methoxyphenyl)pent-2-enoate (4.64)

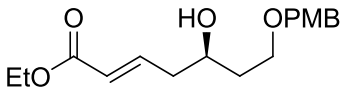


To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), alcohol **4.64a** (41.4 mg, 0.30 mmol, 100 mol%) and (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 0:1 to 3:7) provided the desired linear product **4.64** (60.0 mg, 0.240 mmol) as a colorless oil in 80% yield.

TLC (SiO_2): R_f = 0.25 (ethyl acetate: hexanes, 3:7). **[α]$_D^{25}$** = +25 (c =1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): 7.32 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.26 (dd, *J* = 15.6, 1.8 Hz, 1H), 7.05 – 6.95 (m, 2H), 6.88 (d, *J* = 8.4 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.03 (q, *J* = 6.8 Hz, 1H), 4.17 (q, *J* = 6.8 Hz, 2H), 3.85 (s, 3H), 2.70 – 2.65 (m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.4, 156.3, 145.6, 131.2, 128.7, 126.7, 123.5, 120.9, 110.4, 69.6, 60.2, 55.3, 40.1, 14.3. **FTIR** (neat): 3447, 2937, 2837, 1714, 1652, 1600, 1588, 1490, 1463, 1439, 1392, 1368, 1238, 1189, 1157, 1114, 1040, 977, 936, 782, 753, 706 cm^{-1}. **HRMS** (CI) Calcd. for $C_{14}H_{18}O_4$ $[M-1]^+$: 249.1127, Found: 249.1127. **HPLC**: (Chiralcel AD-H column, hexanes:*i*-PrOH = 92:8, 0.75 mL/min, 230 nm), t_{major} = 21.6 min, t_{minor} = 23.2 min; ee = 86%.

4.4.8 Experiment details of Reaction from Aldehyde Oxidation Level

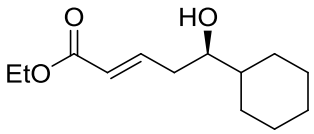
(*R*)-(*E*)-ethyl 5-hydroxy-7-(4-methoxybenzyloxy)hept-2-enoate (4.69)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), freshly distilled aldehyde **4.69b** (58.3 mg, 0.30 mmol, 100 mol%), (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) and isopropyl alcohol (36.1 mg, 0.6 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 24 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:4 to 1:2) provided the branched product (42.5 mg, 0.138 mmol, 1:1 dr) as a colorless oil in 46% yield and the desired linear product **4.69** (17.8 mg, 0.058 mmol) as a colorless oil in 19% yield.

HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 90:10, 1 mL/min, 254 nm), t_{minor} = 10.0 min, t_{major} = 11.1 min; ee = 83%.

(*R*)-(*E*)-ethyl 5-cyclohexyl-5-hydroxypent-2-enoate (4.60)

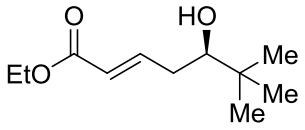


To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), freshly distilled aldehyde **4.60b** (33.6 mg, 0.30 mmol, 100 mol%), (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) and isopropyl alcohol (36.1 mg, 0.6 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography

(SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the branched product (8.0 mg, 0.035 mmol, 1:1 dr) as a colorless oil in 12% yield and the desired linear product **4.60** (51.6 mg, 0.228 mmol) as a colorless oil in 76% yield.

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 90:10, 0.5 mL/min, 254 nm), t_{major} = 14.2 min, t_{minor} = 14.9 min; ee = 92%.

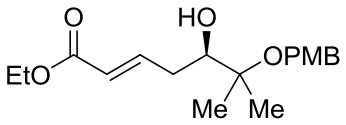
(*R*)-(*E*)-ethyl 5-hydroxy-6,6-dimethylhept-2-enoate (4.62)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), freshly distilled aldehyde **4.62a** (25.8 mg, 0.30 mmol, 100 mol%), (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) and isopropyl alcohol (36.1 mg, 0.6 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20 to 1:10) provided the desired linear product **4.62** (50.9 mg, 0.254 mmol) as a colorless oil in 85% yield.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 0.5 mL/min, 254 nm), t_{minor} = 11.5 min, t_{major} = 12.3 min; ee = 97%.

(*R*)-(*E*)-ethyl 5-hydroxy-6-(4-methoxybenzyloxy)-6-methylhept-2-enoate (4.65)

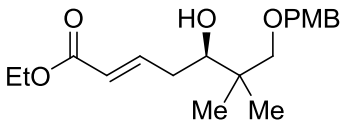


To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), aldehyde **4.65b** (62.5 mg, 0.30 mmol, 100 mol%), (*E*)-ethyl 4-(tert-

butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) and isopropyl alcohol (36.1 mg, 0.6 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 0:100 to 3:7) provided the desired linear product **4.65** (68.0 mg, 0.211 mmol) as a colorless oil in 70% yield.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 96:4, 0.75 mL/min, 210 nm), t_{minor} = 21.6 min; t_{major} = 26.4 min, ee = 99%.

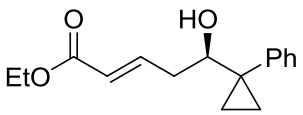
(*R*)-(*E*)-ethyl 5-hydroxy-7-(4-methoxybenzyloxy)-6,6-dimethylhept-2-enoate (4.65)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), aldehyde **4.68b** (66.6 mg, 0.30 mmol, 100 mol%), (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) and isopropyl alcohol (36.1 mg, 0.6 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 0:100 to 3:7) provided the desired linear product **4.68** (84.0 mg, 0.250 mmol) as a colorless oil in 83% yield.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 96:4, 0.75 mL/min, 280 nm), t_{major} = 23.3 min, t_{minor} = 22.4 min; ee = 99%.

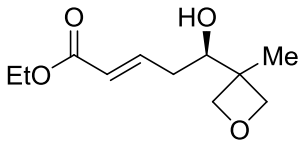
(*R*)-(*E*)-ethyl 5-hydroxy-5-(1-phenylcyclopropyl)pent-2-enoate (4.63)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), aldeyde **4.63b** (43.9 mg, 0.30 mmol, 100 mol%), (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) and isopropyl alcohol (46 36.1 mg, 0.6 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the desired linear product **4.63** (46.7 mg, 0.179 mmol) as a colorless oil in 60% yield.

HPLC: (Chiralcel AD-H column, hexanes:*i*-PrOH = 90:10, 1 mL/min, 254 nm), t_{major} = 8.7 min, t_{minor} = 10.2 min; ee = 93%.

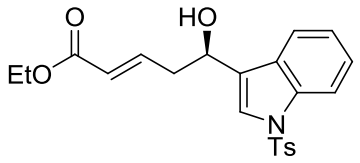
(*R*)-(*E*)-ethyl 5-hydroxy-5-(3-methyloxetan-3-yl)pent-2-enoate (4.66)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), aldehyde **4.66b** (30.0 mg, 0.30 mmol, 100 mol%), (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) and isopropyl alcohol (36.1 mg, 0.6 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:3 to 1:1) provided the desired linear product **4.66** (37.2 mg, 0.174 mmol) as a colorless oil in 58% yield.

HPLC: (Chiralcel OB-H column, hexanes:*i*-PrOH = 95:5, 1 mL/min, 254 nm), t_{minor} = 9.6 min, t_{major} = 11.4 min; ee = 93%.

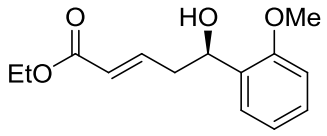
(*R*)-(*E*)-ethyl 5-hydroxy-5-(1-tosyl-1H-indol-3-yl)pent-2-enoate (4.67)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), aldehyde **4.67b** (89.9 mg, 0.30 mmol, 100 mol%), (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) and isopropyl alcohol (36.1 mg, 0.6 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the branched product (20.0 mg, 0.048 mmol, 1:1 dr) as a light brown solid in 16% yield and the desired linear product **4.67** (97.2 mg, 0.235 mmol) as a light brown gummy solid in 78% yield.

HPLC: (Chiralcel AS-H column, hexanes:*i*-PrOH = 90:10, 1.0 mL/min, 254 nm), t_{major} = 11.0 min, t_{minor} = 16.4 min; ee = 96%.

(*R*)-(*E*)-ethyl 5-hydroxy-5-(2-methoxyphenyl)pent-2-enoate (4.64)



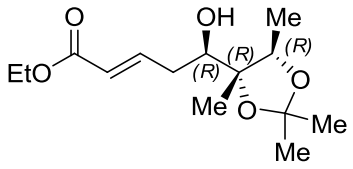
To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), aldehyde **4.64b** (40.8 mg, 0.30 mmol, 100 mol%), (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) and isopropyl alcohol (36.1 mg, 0.6 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2; ethyl

acetate: hexanes, 0:100 to 3:7) provided the desired linear product **4.64** (60.0 mg, 0.240 mmol) as a colorless oil in 80% yield.

HPLC: (Chiralcel OD-H column, hexanes:*i*-PrOH = 90:10, 1 mL/min, 254 nm), t_{major} = 16.9 min, t_{minor} = 18.7 min; ee = 94%.

4.4.9 Experiment Details Catalyst-Directed Diastereoafacial Selection

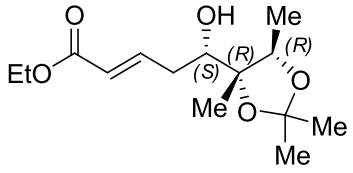
(*R*), (*E*)-ethyl 5-hydroxy-5-[(*4R,5R*)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl]pent-2-enoate (4.71)



To a resealable pressure tube equipped with a magnetic stir bar was added (*R*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), alcohol **4.70** (48.1 mg, 0.30 mmol, 100 mol%) and (*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 72 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the desired linear product **4.71** (55.4 mg, 0.203 mmol) as a colorless oil in 68% yield.

TLC (SiO_2): R_f = 0.25 (ethyl acetate: hexanes, 1:4). **[α]$_D^{25}$** = +11.0 (c = 2.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.01 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.94 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.22 (q, *J* = 6.4 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.67 (dt, *J* = 10.8, 2.8 Hz, 1H), 2.48-2.42 (m, 2H), 2.26-2.17 (m, 1H), 1.45 (s, 3H), 1.36 (s, 3H), 1.29 (t, 3H, *J* = 7.2 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.11 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.3, 145.6, 123.6, 106.9, 83.9, 74.6, 74.4, 60.3, 34.4, 28.7, 26.6, 17.3, 15.6, 14.2. **FTIR** (neat): 3477, 2983, 2938, 2879, 1720, 1654, 1457, 1370, 1324, 1249, 1217, 1190, 1095, 1040, 1000, 979, 909, 860, 818, 721, 680 cm^{-1}. **HRMS** (CI) Calcd. for $C_{14}H_{25}O_5$ $[M+H]^+$: 273.1702, Found: 273.1703.

(*S*), (*E*)-ethyl 5-hydroxy-5-[(*4R,5R*)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl]pent-2-enoate (*epi*-4.71)



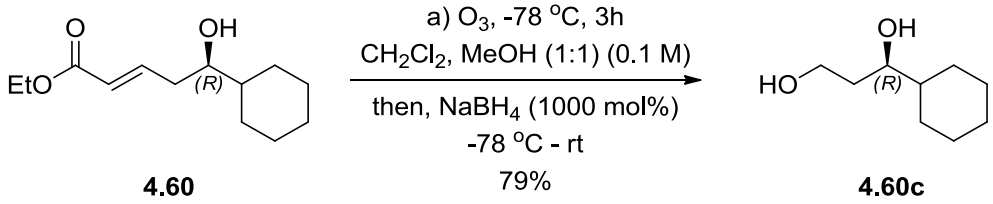
To a resealable pressure tube equipped with a magnetic stir bar was added (*S*)-**I** (16.3 mg, 0.015 mmol, 5 mol%). The tube was sealed with a rubber septum and purged with nitrogen. Dioxane (0.6 mL, 0.5 M), alcohol **4.70** (48.1 mg, 0.30 mmol, 100 mol%) and (E)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate **4.48** (138.2 mg, 0.60 mmol, 200 mol%) were added and the rubber septum was quickly replaced with a screw cap. The mixture was placed in an oil bath at 90 ^{o}C and was allowed to stir for 48 hr. The reaction mixture was concentrated *in vacuo*. Purification of by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10 to 1:5) provided the desired linear product *epi*-**4.71** (46.0 mg, 0.169 mmol) as a colorless oil in 56% yield.

TLC (SiO_2): R_f = 0.24 (ethyl acetate: hexanes, 1:4). $[\alpha]_D^{25}$ = -44.0 (c = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.04 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.92, (dt, *J* = 15.6, 1.6 Hz, 1H), 4.23 (q, *J* = 6.0 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.53 (ddd, *J* = 10.4, 7.6, 3.2 Hz, 1H), 2.44-2.38 (m, 1H), 2.34-2.26 (m, 1H), 2.20 (d, *J* = 7.6 Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.09 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ δ 166.2, 145.5, 123.6, 107.2, 84.4, 74.4, 72.8, 60.2, 35.1, 28.6, 26.8, 17.2, 14.6, 14.2. **FTIR** (neat): 3499, 2984, 2936, 1717, 1654, 1456, 1370, 1321, 1251, 1216, 1178, 1095, 1042, 1008, 979, 929, 862, 822, 714 cm^{-1}. **HRMS** (CI) Calcd. for $C_{14}H_{25}O_5$ $[M+H]^+$: 273.1702, Found: 273.1699.

4.4.10 Determination of Absolute Stereochemistry

The absolute stereochemistry of the vinylogous Aldol-Reformatsky addition product was determined by comparision of the optical rotation with the reported compound. Compound **4.60** was converted to diol 4.**60c** by ozonolysis and $NaBH_4$ reduction of the corresponding ozonide. The specific rotation was in comparision with literature value.[88,89]

$[\alpha]_D^{25}$ = +14.2 (c = 2.6, EtOH), reported +12.3.[16]



4.60 **4.60c**

Chapter 5: Total Synthesis of (+)-Roxaticin *via* Iridium Catalyzed Transfer Hydrogenation Allylation Protocols

5.1 Introduction

Polyketide natural products represent a broad class of secondary metabolites used extensively in human medicine.[90,91] Approximately 20% of the top-selling small molecule drugs are polyketides,[91] and it is estimated that polyketides are five times more likely to possess drug activity compared to other natural product families.[92e] As investigations into polyketide biosynthesis[92] and chemical biology continue to uncover important biological pathways and novel therapeutic targets, the design of synthetic[93] and bio-engineered[94] methods for polyketide construction remains at the forefront of research. Roxaticin is a member of oxopolyene[95] macrolide antibiotic natural product. It was isolated from soil bacteria genus *Steptpmyces*.[96] Roxaticin has interesting biological activities as shown by other members of this class like RK-397 and mycoticin A, the latter being the first isolated member of this class (Figure 5.1).

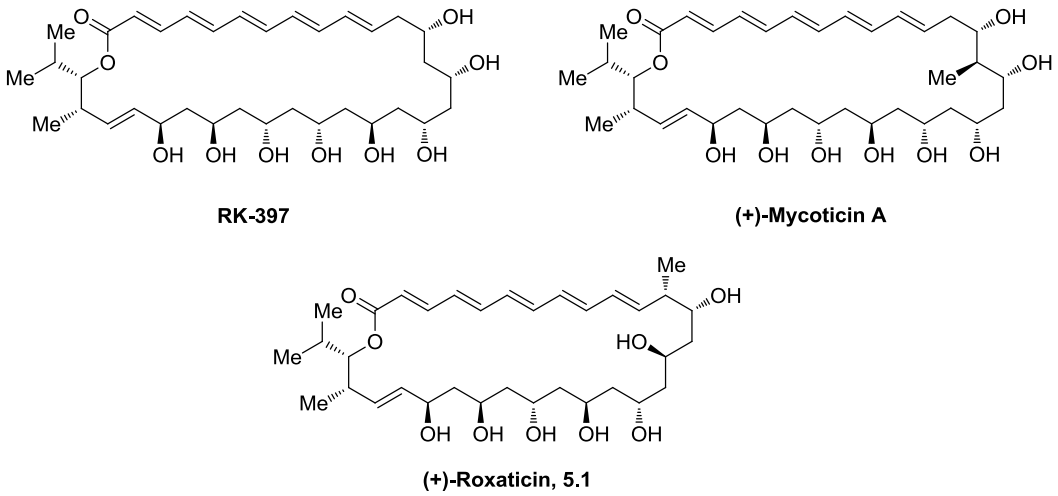


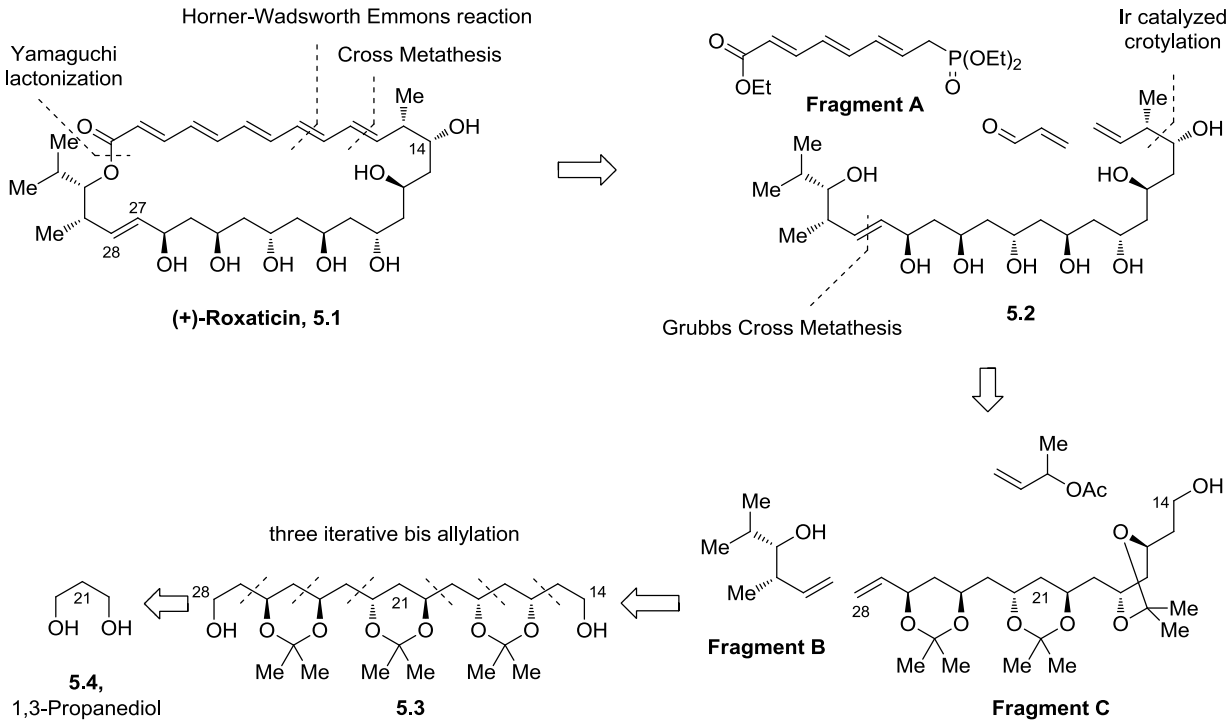
Figure 5.1 Oxo-polyene macrolide natural products.

The complex issues of stereoselectivity posed by polyketides are most often addressed through the use of chiral auxiliaries, chiral reagents and premetallated nucleophiles.[97] Although such methods are highly effective, their use mandates multi-stage preactivation and excessive byproduct generation. Inspired by the atom-economy of asymmetric hydrogenation, we have developed a broad family of C-C bond forming hydrogenations,[98] which provide an alternative to

stoichiometric organometallic reagents in certain carbonyl and imine additions, as we have discussed some of the method in this volume of study. Specially in chapter 3, we have discussed the application of iridium catalyzed carbonyl allylation under transfer hydrogenation condition in the synthesis of 1,3-polyols.[99] Here, we showcase the utility of this methodology in a total synthesis of the oxo-polyene macrolide (+)-roxaticin. Notably, our approach to this complex polyketide is achieved in the absence of chiral reagents or chiral auxiliaries, with minimal use of premetallated *C*-nucleophiles.

5.2 Retrosynthetic Analysis

The retrosynthetic analysis is presented in Scheme 5.1. The macrocyclic ring was formed according to the Yamaguchi lactonization. Installation of the oxopentaene fragment exploited a sequence involving cross metathesis-Horner-Wadsworth-Emmons olefination, which led to fragments **A**, acrolein and **5.2**. C27-28 olefin of **5.2** was prepared using cross metathesis reaction. Elaboration of the protected 1,3-polyol **5.3** to (+)-roxaticin required differential elongation of the homotopic diol termini, which was achieved *via* sequential dehydration-cross-metathesis at C28 and direct carbonyl crotylation from the alcohol oxidation level at C14. Iterative two-directional carbonyl allylation of 1,3- diols was envisioned to deliver the requisite C_2-symmetric 1,3-polyol substructure **5.3**, (Scheme 5.1).



Scheme 5.1 Retrosynthetic analysis of the oxo-polyene macrolide (+) roxaticin.

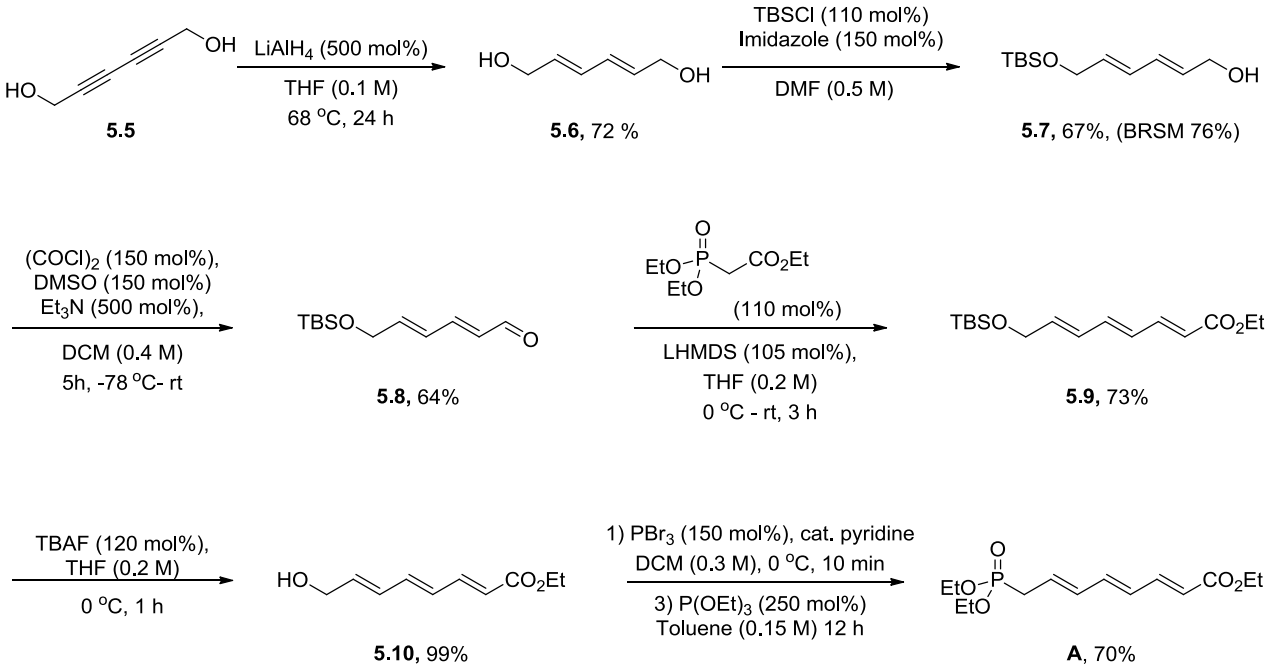
5.3 Synthesis of (+)-Roxaticin

Our approach to (+)-roxaticin takes advantage of carbonyl allylation and crotylation protocols recently developed in our laboratory, wherein primary alcohol dehydrogenation triggers reductive generation of allyliridium nucleophiles, thus enabling asymmetric carbonyl allylation and crotylation directly from the alcohol oxidation level. The convergent synthesis of roxaticin was performed by synthesis of the three fragments **A, B** and **C**.

5.3.1 Synthesis of Fragment A: Triene Phosphonate Ester

The fragment A, phosphonate ester was the Horner-Wadsworth-Emmons intermediate which would desirably couple to the aldehyde prepared from **5.2** and acrolein metathesis product. The fragment A was previously synthesized by Roush in 11 steps, for the synthetic studies towards tetrafibricin.[100] Conversely, we were able to synthesize the same intermediate in 7 steps. Our approach started with $LiAlH_4$ reduction of commercially 1,6-hexadiyne **5.5** to symmetric 2,4-hexadiene-1,6-diol **5.6** in 72% yield. This diol was subjected to TBS protection

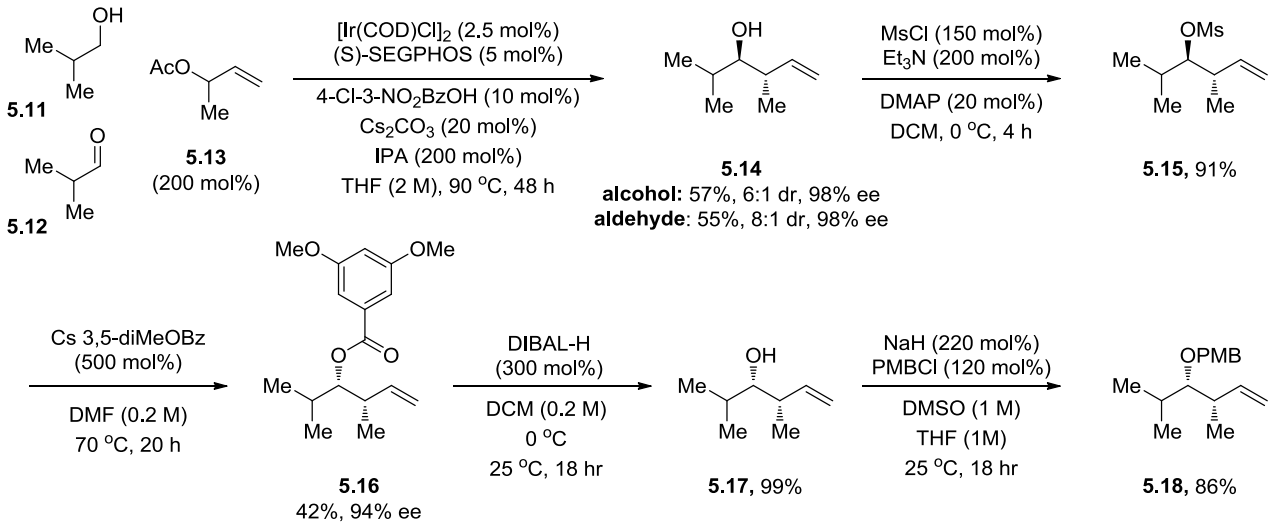
conditions resulted in mono TBS silly ether **5.7** in 67% yield. However, the unreacted starting material was resubmitted to the same conditions for a combined 76% yield. The primary alcohol **5.7** was submitted to Swern oxidation produce aldehyde **5.8** in 64% yield. For synthesis of fragment A, from this point onwards, all reactions were performed in dark due to instability of polyene part. The aldehyde was subjected to Horner-Wadsworth-Emmons olefination conditions with triethyl phosphonoacetate and LiHMDS, the reaction afforded intermediate trienoate ester **5.9** in 73% yield. Deprotection of silyl ether **5.9** using TBAF in THF afforded alcohol **5.10** in quantitative yield. The alcohol **5.10** is a solid and can be store in freezer in dark. This allylic alcohol **5.10** was subjected to brominating condition, resulting in allylic bromide using PBr_3. The allylic bromide was very unstable and was directly treated with triethylphosphite and catalytic pyridine, in refluxing toluene to produce the phosphonate fragment A in 70% yield over two steps (Scheme 5.2).



Scheme 5.2 Synthesis of phosphonate ester, fragment A.

5.3.2 Synthesis of Fragment B: *syn*-Crotyl Alcohol

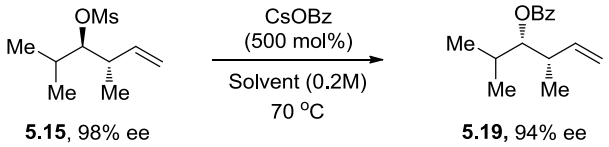
The fragment B is essentially a *syn*-crotylation product of isobutyraldehyde. As discussed earlier our approach to (+)-roxaticin takes advantage of carbonyl allylation and crotylation protocols[10] developed in our laboratory, wherein primary alcohol dehydrogenation triggers reductive generation of allyliridium nucleophiles, thus enabling asymmetric carbonyl allylation and crotylation directly from the alcohol oxidation level. This redox economy can be utilized in proficient synthesis of roxaticin. The synthesis of fragment B commence with the crotylation of the *iso*-butyralalcohol to give the crotyl product **5.14** in 57% yield and 6:1 dr and 98% ee. However, we found out that crotylation of *iso*-butyraldeyde in the presence of *iso*-propyl alcohol (200 mol%) as reductant resulted in higher *anti*-diastereoselectivity (8:1) than *iso*-butyralalcohol (6:1).These finding are in accordance with previous findings form our laboratory.[10e] Nevertheless, to get right *anti*-diastereomer, the alcohol has to be inverted. Before long, we found out that any variation of Mitsunobu inversion was not fruitful, possibly due to the steric hindrance of the two contiguous isopropyl group on each side of reacting alcohol. On the other hand, it was possible to perform substitution on the corresponding mesylate. The crotyl alcohol **5.14** was converted to mesylate **5.15** in 91% yield using standard mesylation condition (Scheme 5.3). Treatment of this mesylate with cesium benzoate resulted in substitution product **5.16** in slightly inferior yield, and more importantly with minimal enantiomeric erosion (Table 5.1)



Scheme 5.3 Synthesis of fragment B.

It was unsuccessful to optimization the substitution of **5.15** using cesium benzoate, by changing reaction conditions. The solvent screening however, displayed the reaction is slightly faster in DMF (Table 5.1). Increase in reaction temperature result in elimination pathway.

Table 5.1 Solvent effect on substitution on mesylate 5.15.



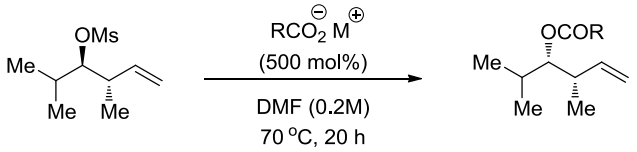
5.15, 98% ee

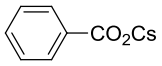
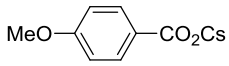
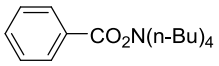
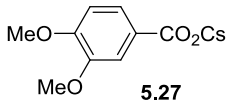
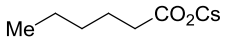
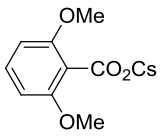
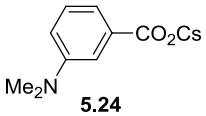
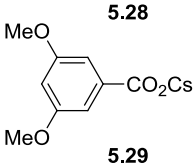
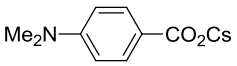
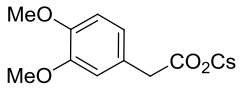
5.19, 94% ee

Solvent	Time (hr)	Yield (%)
DMF	40	26
DMSO	48	23
1,3-DiMe-2-imidazolidine, **5.20**	48	29

Additionally, the nucleophilic partner cesium benzoate salts were screened. The introduction of electron donating substitution at benzoate resulted in improvement in the product yield. The 3- *N*,*N*-dimethylbenzoate **5.24** and 4-*N*,*N*-dimethylbenzoate **5.25** both resulted in 39% product yield (Table 5.2, entries 4 and 5). However, the same effect was not true for methoxy substituent. Cesium 4-methoxybenzoate gave poor yield **5.26** while 3,4-dimethoxybenzoate gave slightly higher yield **5.27** (Table 5.2, entries 6 and 7). As the electron donating substituent at 3-position resulted in slight improvement the 3,5-dimethoxybenzoate **5.29** resulted in higher yield (42%) among the nucleophile screened (Table 5.2, entry 9). The 2,6-dimethoxybenzoate **5.28** on the other hand, gave slightly lowered yield possibly due to steric hindrance. The benylic and aliphatic cesium benzoate **5.23** and **5.30** was not as effective.

Table 5.2 Effect of different cesium benzoate on substitution.

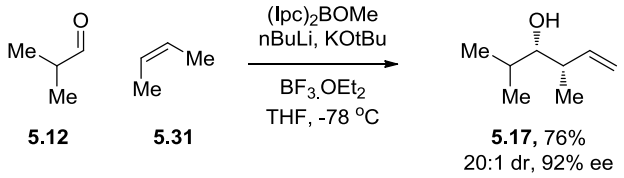


Entry	Nucleophile	Yield (%)	Entry	Nucleophile	Yield (%)
1	 **5.21**	24	6	 **5.26**	21
2	 **5.22**	37	7	 **5.27**	33
3	 **5.23**	28	8	 **5.28**	31
4	 **5.24**	39	9	 **5.29**	42
5	 **5.25**	39	10	 **5.30**	33

We were able to utilized the benzoate as protecting group, however, later in the synthesis, we found out that it was not effective and we needed to use PMB ether as protecting alcohol in fragment B. We were able to perform protecting group exchange by DIBAL reduction of 3,5-dimethoxybenzoate in quantitative yield. Treatment of the corresponding crotyl alcohol with PMBCl and NaH provided the desire fragment B, **5.18**, in 86% yield (Scheme 5.3).

As we witnessed this approach requires inversion of the crotyl alcochol to acquire the correct *syn*-diastereoselectivity and protection-deprotection sequence increases the number of steps, this no longer remains a desirable route. The same fragment B has been synthesized before using Brown crotylation method.[101] We were able to reproduce the same conditions in our laboratory. PMB protection resulted in the fragment B in two steps. Recently, our research group

has devoted studies towards development of *syn*-crotylation protocols[102] which would enable us to provide a second generation synthesis of fragment B.

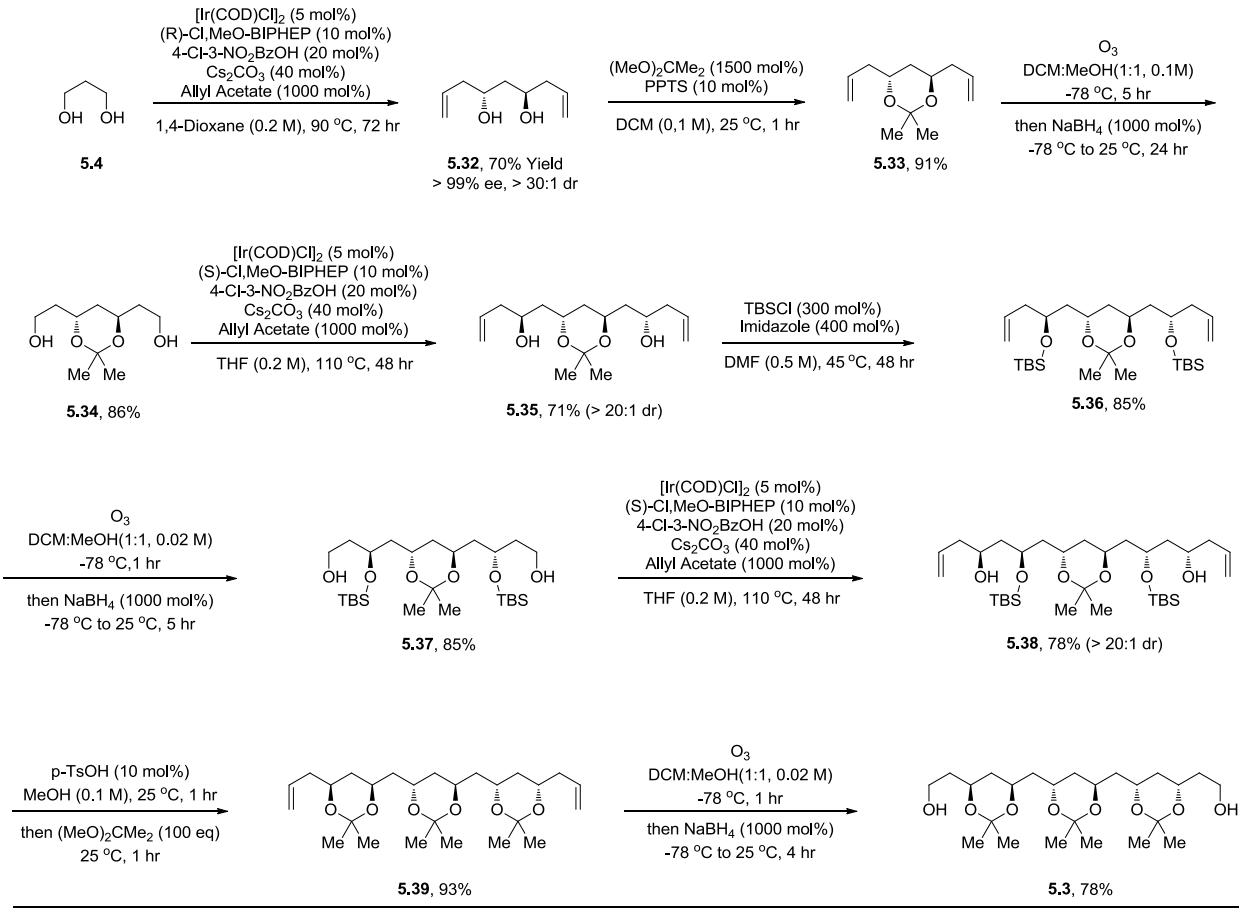


Scheme 5.4 Brown crotylation in synthesis of syn-crotyl fragment B.

5.3.3 Synthesis of Fragment C: Polyol Fragment

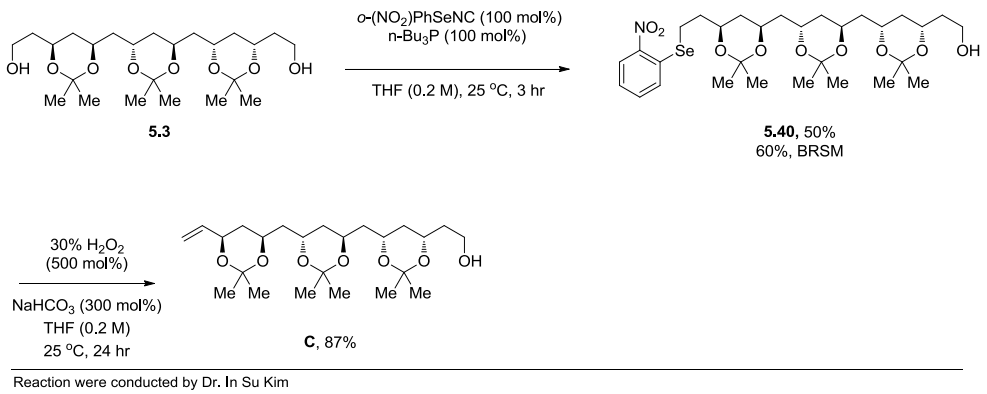
Two directional bis *C*-allylation was conducted with 1,3-propanediol with the *ortho*-cyclometalated iridium *C,O*-benzoate **(*R*)-I** generated *in situ* from [Ir(cod)Cl]2, (*R*)-Cl,MeO-BIPHEP, 4-chloro-3- nitrobenzoic acid, and allyl acetate, double allylation product **5.32** was isolated in 70% yield and >99% ee. Conversion of **5.32** to acetonide **5.33** followed by ozonolysis of the olefinic termini provides the homologous diol **5.34**, constituting "one iteration" of two-directional carbonyl allylation from the alcohol oxidation level. In subsequent iterations of two-directional carbonyl allylation, ozonolysis reactions were quenched with $NaBH_4$ to furnish the homologous diols. In large scale ozonolysis reactions, $NaBH_4$ reduction of the ozonide is preferred as this protocol circumvents generation of stoichiometric organic byproducts; hence, facilitates product purification.

Subsequent iteration of two-directional carbonyl allylation of **5.34** was conducted. Double allylation product **5.35** was produced in 71% yield and >20:1 dr. Protection with TBS group (**5.36**) followed by ozonolysis generated diol **5.37**, which was ready for the third carbonyl bisallylation reaction. The final bis-allylation produced bis-homoallylic alcohol **5.38** in 78% and >20:1 dr. Protecting group exchange (**5.39**) followed by ozonolysis furnished three acetonide protected diol **5.3**. With all three iterations of two-directional allylation, complete levels of catalyst-directed diastereoselectivity were observed, providing rapid access to the acetonide-protected C_2-symmetric 1,3-polyol **5.3** as a single diastereomer. Thus, *tris*acetonide **5.3**, which possesses six stereocenters, was prepared in only nine steps from 1,3-propanediol (Scheme 5.5).



Scheme 5.5 Synthesis of *tris*acetonide fragment using three iteration of iridium catalyzed bisallylation reaction.

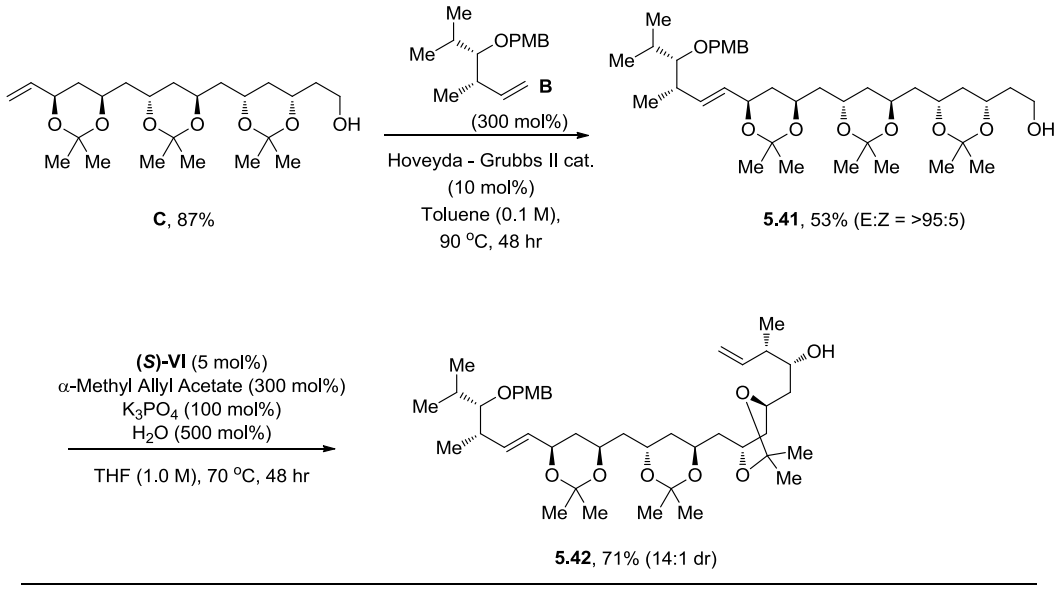
Differentiation of diol temini of *tris*-acetonide **5.3** was required. Grieco's two-step method[103] for primary alcohol dehydration was conducted. Because the diol termini of **5.3** are homotopic, the selenylation product appeared as a component of a statistical mixture with 1.1 eq of *O*-(NO_2)PhSeCN. Mono-selenide **24** was obtained in 50% yield along with the formation of diselenide in 18% yield. Recovered starting material **5.3** (21%) was re-submitted to the second round of the reaction. The combined yield of the two reactions was 60%. The second elimination step was very sensitive to base and the amount of H_2O_2, $NaHCO_3$ appeared to be the best base additive afforded the desired product **25** in 87% yield (Scheme 5.6).



Scheme 5.6 Synthesis of fragment **C** in total synthesis of (+)-roxaticin.

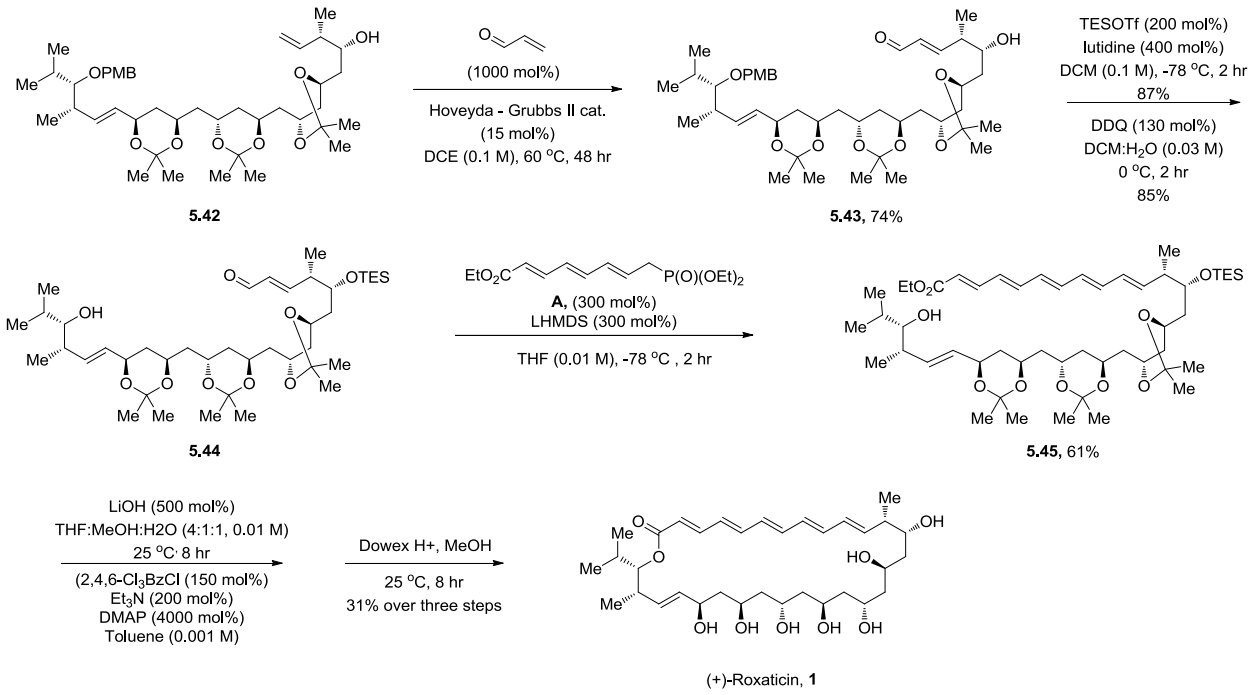
5.3.4 End Game: Combing Fragments

Once we have all fragments in hand, cross metathesis was attempted with the previously prepared homoallylic ether fragments C and B with various catalytic systems. Hoveyda-Grubbs II catalyst With 10 mol% of loading, 53% of cross coupling product **5.41** was obtained in DCM at 40 ^{o}C. Direct carbonyl crotylation from the alcohol oxidation level at C14 using the preformed iridium *C,O*-benzoate complex **(*S*)-II** delivered the desired adduct **27** in 85% yield with 14:1 *anti*-diastereoselectivity, (Scheme 5.7).



Scheme 5.7 Combination of fragment **B** and **C** by cross methathesis and crotylation of the **5.41**.

With homoallylic alcohol **5.42** in hand, installation of the polyene substructure was undertaken. The unprotected homoallylic alcohol **5.42** was subjected to cross metathesis with acrolein to deliver the corresponding enal **5.43** in 74% yield (BRSM) with complete (*E*)-selectivity as determined by ^{1}H NMR.[104] TES protection and DDQ deprotection of PMB ether resulted in hydroxyl enal **5.44.** Exposure of the enal **5.44** to the previously reported Horner-Wadsworth-Emmons intermediate fragments A, delivered polyunsaturated ester **5.45** in 61% yield. Ester hydrolysis followed by Yamaguchi lactonization and global deprotection, as practiced in prior syntheses by Mori and Evans, were attempted to deliver (+)-roxaticin. This three-step sequence delivered (+)-roxaticin in 31% yield, (Scheme 5.8).



Scheme 5.8 End game of synthesis of (+)-roxaticin.

5.4 Summary

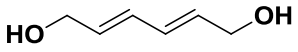
In summary the total synthesis of (+)-roxaticin was possible using the iterative bisallylation to construct the C_2-symmetric 1,3-polyol substructure C14−C28 unit of roxaticin. This fragment was elaborated to roxaticin employing transformation that resulted in functional

groups that were directly compatible with the next transformation, e.g. alcohols were directly reacted under iridium catalyzed crotylation reaction and alkenes were subjected to cross metathesis. (+)-Roxaticin is prepared from 1,3-propane diol in 20 longest linear steps and a total number of 29 manipulations. In this approach, nine of ten C-C bonds formed in the longest linear sequence was made *via* metal catalysis, including 7 C-C bonds formed *via* iridium catalyzed alcohol C-C coupling. This approach bypasses the redox manipulations and use of any chiral auxiliary. Notably, this total synthesis represents the most concise preparation of any oxo-polyene macrolide reported to date, and is achieved in the absence of chiral reagents, chiral auxiliaries and with minimal use of premetallated *C*-nucleophiles.

5.5 Experimental Section

5.5.1 Fragment A: Experimental Details and Spectral Data

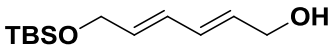
(2*E*,4*E*)-hexa-2,4-diene-1,6-diol (5.6)



Literature procedure was followed. To a stirred solution of 1,6-hexadiyne **5.5** (1 g, 9.08 mmol, 100 mol%) in THF (100 mL, 0.09 M) at 0 ^{o}C was added $LiAlH_4$ (1.72 g, 45.41 mmol, 500 mol%) in four portions. The reaction mixture was stirred at 0 ^{o}C for 30 min and heated to reflux for 24 h. The reaction mixture was diluted with ether (100 mL) and carefully quench with H_2O (2 mL), 15% aqueous NaOH (2 mL) and H_2O (5 mL). The suspension is filtered through celite and the residue was rinsed with ethyl acetate. The filterate is dried over $MgSO_4$, concentrated in vacuo to give the desire diol **5.6** (0.88g, 7.74 mmol) as white solid in 85 % yield.

^{1}H NMR [(400 MHz, ($CD)_3CO$)]: δ 6.27-6.19 (m, 2H), 5.81-5.71 (m, 2H), 4.09 (brs, 4H), 3.78 (s, 2H). **^{13}C NMR** [100 MHz,($CD)_3CO$)]: δ 133.9, 130.2, 62.8. **FTIR** (neat): υ 3484, 1726, 1712, 1242, 1030, 991, 889, 671 cm^{-1}. **HRMS** (CI) Calcd. for $C_6H_{11}O_2$ $[M+H]^+$: 115.0759, Found: 115.0762.

(2*E*,4*E*)-6-(tert-butyldimethylsilyloxy)hexa-2,4-dien-1-ol (5.7)

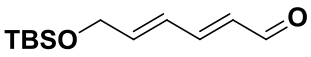


To a stirred solution of imidazole (1.23 g, 18.07 mmol, 150 mol%) in DMF (24 mL, 0.75 M) was dropwise added solution of diol **5.6** (2.05 g, 12.05 mmol, 100 mol%) in DMF (5 mL, 2.4 M) at ambient temperature. The reaction mixture was stirred for 45 min. TBSCl (1.99 g, 13.25 mmol, 110 mol%) was added to reaction mixture in one portion. The reaction mixture was stirred for 20 h at ambient temperature. H_2O (25 mL) was added to reaction mixture and the resulting solution was extracted with ether (50 mL x 3). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by

column chromatography (SiO_2: ethyl acetate:hexanes, 1:10 to 1:4) to give the mono protected diol **5.7** (1.85 g, 8.10 mmol) as a colorless liquid in 67% yield.

TLC (SiO_2): R_f = 0.45 (ethyl acetate:hexanes, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.26-6.16 (m, 2H), 5.80-5.70 (m, 2H), 4.19 (d, *J* = 4.8 Hz, 2H), 4.13 (d, *J = 7.0* Hz, 2H), 1.84 (br s, 1H), 0.88 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 132.9, 131.5, 130.7, 128.9, 63.3, 63.1, 25.9, 18.3, -5.3. **FTIR** (neat): υ 3355, 2958, 2954, 2929, 2883, 2856, 1471, 1463, 1370, 1361, 1254, 1109, 1081, 987, 774, 672 cm^{-1}. **HRMS** (CI) Calcd. for $C_{12}H_{25}O_{2Si}$ $[M+H]^+$: 229.1624, Found: 229.1620.

(2*E*,4*E*)-6-(tert-butyldimethylsilyloxy)hexa-2,4-dienal (5.8)

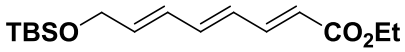


To a stirred solution of oxalyl chloride (1.2 mL, 13.79 mmol, 150 mol%) in DCM (35 mL, 0.4 M) at -78 ^oC was added DMSO (1 mL, 13.79 mmol, 150 mol%). The reaction mixture was allowed to stir for 20 min at -78 ^oC. The alcohol **5.7** (2.1 g, 9.19 mmol, 100 mol%) in DCM (12 mL, 0.75 M) was added to reaction mixture and the resulting solution was allowed to stir for 30 min at -78 ^oC. Triethylamine (6.4 mL, 45.97 mmol, 500 mol%) was added to the reaction mixture. The resulting solution was allowed to stir for 30 min at -78 ^oC, warmed to ambient temperature and stirred for 5 hr. The reaction was quenched with H_2O (40 mL) and extracted with DCM (80 mL x 3). The combined organic phase was washed with H_2O (40 mL), brine (40 mL), dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:10 with 0.1% TEA) to give the aldehyde **5.8** (1.33 g, 5.87 mmol) as a slightly yellow oil in 64% yield.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.53 (d, *J* = 8.0 Hz, 1H), 7.10 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.56-6.49 (m, 1H), 6.29 (dt, *J* = 14.8, 4 Hz, 1H), 6.11 (dd, *J* = 15.6, 7.6 Hz, 1H), 4.31 (dd, *J* = 4.0, 2.0 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.7, 151.6, 144.3, 131.1, 126.6, 62.7, 25.8, 25.6, -5.5. **FTIR** (neat): υ 2954, 2929, 2883, 2856, 2722, 1682, 1644, 1602, 1471, 1445, 1377, 1352, 1252, 1161,

1131, 1010, 986, 960, 809, 775, 675. **HRMS** (CI) Calcd. for $C_{12}H_{23}O_2Si$ $[M+H]^+$: 227.1467, Found: 227.1467.

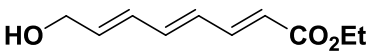
(2*E*,4*E*,6*E*)-ethyl 8-(tert-butyldimethylsilyloxy)octa-2,4,6-trienoate (5.9)



To a stirred solution of the triethyl phosphonoacetate (2.9 mL, 14.48 mmol, 110 mol%) in THF (66 mL, 0.22 M) was added LiHMDS (1M solution in THF, 13.8 mL, 13.82 mmol, 105 mol%) at 0 ^oC and the reaction mixture was stirred for 20 min. The aldehyde **5.8** (3 g, 13.16 mmol, 100 mol%) in THF (10 mL, 1.3 M) was added dropwise to reaction mixture at 0 ^oC. The reaction mixture was warmed to ambient temperature in 3 hr, quenched with saturated aq. NH_4Cl (50 mL) and extracted with ether (100 mL x 3). The combined organic phase was washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: diethyl ether:hexanes, 1:20 to 1:10 with 0.1% TEA) to give the ester **5.9** (2.85 g, 9.61 mmol) as a colorless oil in 73% yield.

TLC (SiO_2): R_f = 0.35 (diethyl ether:hexanes, 1:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.56 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.39-6.31 (m, 1H), 6.28 (dd, *J* = 14.0, 10.4 Hz, 1H), 5.97 (dt, *J* = 15.2, 4.8, Hz, 1H), 5.86 (d, *J* = 15.2 Hz, 1H), 4.27 (d, *J* = 4.4 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.1, 144.5, 140.1, 137.7, 129.3, 128.5, 120.7, 63.1, 60.2, 25.9, 18.4, 14.3, -5.3. **FTIR** (neat): υ 2954, 2929, 2885, 2856, 1704, 1637, 1618, 1471, 1377, 1338, 1294, 1272, 1247, 1098, 1014, 977, 941, 892, 776, 744, 716, 666. **HRMS** (CI) Calcd. for $C_{16}H_{29}O_3Si$ $[M+H]^+$: 297.1886, Found: 297.1890.

(2*E*,4*E*,6*E*)-ethyl 8-hydroxyocta-2,4,6-trienoate (5.10)

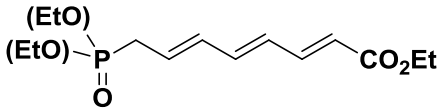


To a stirred solution of ester **5.9** (2.52 g, 8.49 mmol, 100 mol%) in THF (42 mL, 0.2 M) was added TBAF (1M solution in THF, 10.2 mL, 10.2 mmol, 120 mo%) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 1 hr and Ethyl acetate (200 mL) was added. The the organic layer

was washed with H_2O (50 mL x 2), brine (50 mL) and dried with Na_2SO_4. The organic phase was concentrated in vacuo and the residue was was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:1 with 0.1% TEA) to give the alcohol **5.10** (1.50 g, 8.32 mmol) as a white solid in 98% yield.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (dd, *J* = 15.2, 11.6 Hz, 1H), 6.54 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.36-6.24 (m, 2H), 6.00 (dt, *J* = 14.8, 5.6 Hz, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 4.27 (d, *J* = 4.8 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.35 (br s, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.1, 144.3, 139.8, 137.1, 129.8, 129.6, 121.0, 62.7, 60.3, 14.2. **FTIR** (neat): υ 3303, 3199, 3017, 2993, 2901, 2951, 1705, 1615, 1588, 1479, 1444, 1336, 1260, 1214, 1179, 1132, 1086, 967, 915, 876, 843, 814, 778, 747, 715, 692. **HRMS** (CI) Calcd. for $C_{10}H_{15}O_3$ $[M+H]^+$: 183.1021, Found: 183.1025.

(2E,4E,6E)-ethyl 8-(diethoxyphosphoryl)octa-2,4,6-trienoate (A)



To a stirred solution of the alcohol **5.10** (570 mg, 3.13 mmol, 100 mol%) in DCM (11 mL, 0.3 M) was added pyridine (30 μL, 0.38 mmol, 12 mol%) followed by PBr_3 (1M solution in DCM, 4.7 mL, 4.70 mmol, 150 mol%) at 0 ^oC for 10 min. The reaction was quenched with water (20 mL) and extracted with ether (20 mL x 3). The combined organic phase was washed with water (20 mL), saturated aq. $NaHCO_3$ (30 mL), brine (30 mL), dried with Na_2SO_4, filtered and concentrated in vacuo to give allylic bromide as white semi solid which was used without any further purification.

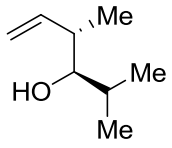
The allylic bromide was dissolved in toluene (21 mL, 0.15 M) and triethylphosphite (1.35 mL, 7.82 mmol, 250 mol%) was added. The reaction mixture was heated at reflux for 12 hr. Ethyl acetate (21 mL) was added and the reaction mixture was washed with water (20 mL x 3) and brine (20 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 3:1 to 5:1) to

give the desire phosphonate ester **A** (662 mg, 2.189 mmol) as a light yellow semi solid in 70% yield over two steps.

TLC (SiO_2): R_f = 0.30 (ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.48 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.31-6.23 (m, 2H), 5.83 (d, *J* = 15.6 Hz, 1H), 5.87-5.81 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.15-4.07 (m, 4H), 2.65 (dd, *J* = 23.2, 7.6 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 6H), 1.28 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.0, 144.1 (d, *J* = 12 Hz), 139.6 (d, *J* = 20.8 Hz), 134.3 (d, *J* = 59.6 Hz), 129.7 (d, *J* = 20.8 Hz), 127.2 (d, *J* = 53.6 Hz), 121.3, 62.1 (d, *J* = 26.8 Hz), 60.3, 31.9, 30.5, 16.5, 16.4, 14.3. **FTIR** (neat): υ 3443, 2982, 2828, 2901, 1704, 1632, 1618, 1584, 1445, 1368, 1393, 1231, 1188, 1148, 1133, 1018, 961, 894, 844, 786, 714. **HRMS** (CI) Calcd. for $C_{14}H_{24}O_5P$ $[M+H]^+$: 303.1361, Found: 303.1363.

5.5.2 Fragment B: Experimental Details and Spectral Data

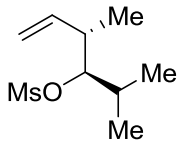
(3*R*,4*S*)-2,4-Dimethylhex-5-en-3-ol (5.14)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (33.6 mg, 0.05 mmol, 2.5 mol%), (*S*)-SEGPHOS (61.1 mg, 0.1 mmol, 5 mol%), Cs_2CO_3 (0.13 g, 0.4 mmol, 20 mol%) and 4-cyano-3-nitrobenzoic acid (38.4 mg, 0.2 mmol, 10 mol%) was added THF (1.0 mL) followed by acetic acid 3-buten-2-yl ester (0.46 g, 4.0 mmol, 200 mol%). The reaction mixture was allowed to stir at 90 ^oC for 0.5 hr and cooled to ambient temperature. Isobutyraldehyde **5.12** (0.183 mL, 2.0 mmol, 100 mol%) in THF (1.0 mL) and isopropanol (0.3 mL, 4.0 mmol, 200 mol%) were added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^oC for 48 hr. The reaction mixture, without the removal of solvent, was passed through silica gel (elution with diethyl ether:pentane, 1:10) and carefully concentrated. The residue was purified by distillation (bp = 155-170 ^oC) to give **5.14** (0.141 g, 1.100 mmol, *anti*:*syn* = 8:1) as a colorless oil in 55% yield.

TLC (SiO_2): R_f = 0.35 (diethyl ether:pentane, 1:10). **$[\alpha]_D^{26}$** = +76.7 (*c* = 0.3, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.82-5.72 (m, 1H), 5.13-5.07 (m, 2H), 3.07 (dd, *J* = 10.4, 4.8 Hz, 1H), 2.35-2.29 (m, 1H), 1.76-1.71 (m, 1H), 1.50 (d, *J* = 4.4 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 140.7, 116.4, 79.6, 41.6, 30.5, 20.1, 17.2, 16.6. **FTIR** (neat): υ 3419, 3075, 2960, 2931, 2872, 1460, 1413, 1382, 1240, 1171, 1131, 1086, 963, 950, 910, 850, 811 cm^{-1}. **Chrial GC**: Enantiomeric excess was determined by chiral GC using Cyclosil-B (30 m, Inter diameter 0.320 mm and film 0.25 μm) column using method 50 ^oC for 3 min and 50 – 200 ^oC increasing 10 ^oC/min for 15 min. t_{major} = 8.43 min, t_{minor} = 8.51 min; ee = 96%.

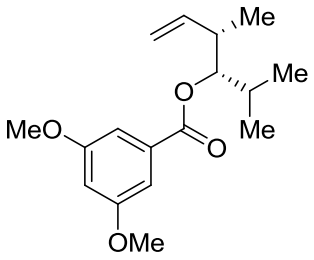
(3*R*,4*S*)-2,4-Dimethylhex-5-en-3-yl methanesulfonate (5.15)



To a stirred solution of the alcohol **5.14** (50 mg, 0.390 mmol) in DCM (2.0 mL) were added methanesulfonyl chloride (45 μL, 0.585 mmol), Et_3N (0.11 mL, 0.780 mmol) and DMAP (9.5 mg, 0.078 mmol) at 0 ^oC. The reaction mixture was stirred for 4 hr at ambient temperature, and then quenched with H_2O (1 mL). The resulting solution was extracted with DCM (10 mL × 2). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:20 to 1:10 with 0.1% TEA) to give **5.15** (73.4 mg, 0.356 mmol) as a colorless oil in 91% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:10). **$[\alpha]_D^{26}$** = +53.3 (*c* = 0.6, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.84-5.74 (m, 1H), 5.15-5.07 (m, 2H), 4.45 (t, *J* = 6.0 Hz, 1H), 3.03 (s, 3H), 2.61-2.55 (m, 1H), 2.04-1.94 (m, 1H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 139.7, 116.4, 92.5, 40.9, 39.2, 30.2, 20.0, 18.1, 17.7. **FTIR** (neat): υ 2970, 2936, 2879, 1743, 1465, 1417, 1332, 1170, 999, 971, 840, 805 cm^{-1}. **HRMS** (CI) Calcd. for $C_9H_{19}O_3S$ $[M+H]^+$: 207.1055, Found: 207.1056.

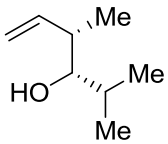
(3*S*,4*S*)-2,4-Dimethylhex-5-en-3-yl 3,5-dimethoxybenzoate (5.16)



To a stirred solution of the mesylate **5.15** (0.5 g, 2.424 mmol) in DMF (12.1 mL) was added cesium 3,5-dimethoxybenzoate (3.8 g, 12.12 mmol) at ambient temperature. The reaction mixture was stirred for 20 hr at 70 ^{o}C, and then quenched with H_2O (5 mL). The resulting solution was extracted with EtOAc (20 mL × 2). The combined organic extracts were washed with brine (10 mL × 2), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:50 to 1:20 with 0.1% TEA) to give **5.16** (0.30 g, 1.026 mmol) as a colorless oil in 42% yield.

TLC (SiO_2): R_f = 0.48 (ethyl acetate:hexanes, 1:10). $[\alpha]_D^{26}$ = +44.0 (*c* = 0.5, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21-7.19 (m, 2H), 6.66-6.63 (m, 1H), 5.79-5.69 (m, 1H), 5.09 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.01 (dd, *J* = 10.4, 1.2 Hz, 1H), 3.82 (s, 6H), 2.63-2.56 (m, 1H), 2.06-2.00 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.5, 160.9, 140.6, 132.7, 115.3, 107.5, 105.4, 81.6, 55.8, 40.2, 30.0, 20.0, 16.8, 15.8. **FTIR** (neat): υ 2965, 2932, 2869, 2839, 1716, 1644, 1595, 1457, 1427, 1387, 1352, 1323, 1299, 1230, 1204, 1101, 1048, 998, 979, 952, 914, 844 cm^{-1}. **HRMS** (CI) Calcd. for $C_{17}H_{25}O_4$ $[M+H]^+$: 293.1753, Found: 293.1751.

(3*S*,4*S*)-2,4-dimethylhex-5-en-3-ol (5.17)

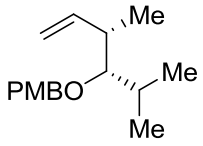


To a stirred solution of the ester **5.16** (1.93 g, 6.60 mmol, 100 mol%) in DCM (33 mL, 0.2 M) was dropwise added neat DIBAL (2.82 g, 19.80 mmol, 300 mol%) at -78 ^{o}C. The reaction

mixture was stirred for 1 hr at 70 ^{o}C and allowed to warm to ambient temperature for 12 h. The reaction mixture was cooled to 0 ^{o}C and carefully quenched with MeOH (3 mL) and stirred at amient temperature for 15 min. The reaction mixture was filtered through celite and carefully concentrated. The residue was purified by column chromatography (SiO_2: ether:pentane, 1:20 to 1:15) to give **5.17** (0.83 g, 6.47 mmol) as a colorless oil in 98% yield.

TLC (SiO_2): R_f = 0.40 (ether:pentane, 1:15). $[\alpha]_D^{26}$ = -35.0 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.83-5.75 (m, 1H), 5.10-5.04 (m, 2H), 3.16 (dd, *J* = 5.8 Hz, 1H), 2.36 (m, 1H), 1.75 (m, 1H), 1.38 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.8, 3H), 0.92 (d, *J* = 6.8, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ141.8, 114.6, 79.4, 40.5, 30.4, 19.5, 17.1, 13.4. **FTIR** (neat): υ 3388, 3077, 2962, 2932, 2905, 2874, 1641, 1460, 1419, 1383, 1368, 1286, 1236, 1087, 981, 960, 846, 758 cm^{-1}. **HRMS** (CI) Calcd. for $C_8H_{17}O$ $[M+H]^+$: 129.1279, Found: 129.1277. **Chrial GC**: Enantiomeric excess was determined by chiral GC using Cyclosil-B (30 m, Inter diameter 0.320 mm and film 0.25 μm) column using method 50 ^{o}C for 3 min and 50 – 200 ^{o}C increasing 10 ^{o}C/min for 15 min. t_{major} = 8.84 min, t_{minor} = 8.95 min; ee = 92%.

1-(((3*S*,4*S*)-2,4-dimethylhex-5-en-3-yloxy)methyl)-4-methoxybenzene (5.18, B)

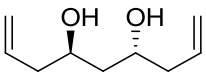


Literature procedure was followed[3]. To sodium hydride (0.41 g of 60% suspension in mineral oil, 10.16 mmol, 220 mol%) suspension in DMSO (10 mL, 1M) was added the alcohol **5.17** (0.59 g, 4.62 mmol, 100 mol%) in THF (4 mL, 1.1 M) at ambient temperature which resulted in brown color solution. The reaction mixture was stirred for 30 min. PMBCl (0.87 g, 5.54 mmol, 120 mol%) was added and allowed to stirred for 12 hr. The reaction was quenched with brine (30 mL) and extracted with ether (50 mL x 2). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ether:hexanes, 1:100 to 1:50) to give the product **5.18, B** (0.98 g, 3.97 mmol) as a colorless oil in 86% yield.

TLC (SiO_2): R_f = 0.35 (ether:hexanes, 1:20). **$[\alpha]_D^{26}$** = +15.0 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.88-5.5.80 (m, 1H), 5.05 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 4.99-4.96 (m, 1H), 4.54 (d, *J* = 10.2 Hz, 1H), 4.49 (d, *J* =10.2 Hz, 1H), 3.81 (s, 3H), 3.01 (t, *J* = 5.4 Hz, 1H), 2.47-2.43 (m, 1H), 1.88-1.83 (m, 1H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.2, 142.7, 131.5, 129.2, 113.7, 113.6, 88.4, 74.9, 55.3, 41.1, 31.0, 20.4, 17.5, 15.4. **FTIR** (neat): υ 3070, 2959, 2928, 2905, 2870, 2835, 1633, 1613, 1513, 1463, 1420, 1350, 1301, 1171, 1109, 1086, 1062, 1037, 998, 957, 911, 821, 755, 681. **HRMS** (CI) Calcd. for $C_{16}H_{25}O_2$ $[M+H]^+$: 249.1854, Found: 249.1855.

5.5.3 Fragment C: Experimental Details and Spectral Data

(4*R*,6*R*)-Nona-1,8-diene-4,6-diol (5.32)

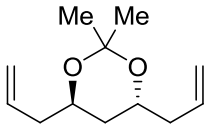


To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (1.35 g, 2.012 mmol, 5 mol%), (*R*)-Cl,MeO-BIPHEP (2.61 g, 4.008 mmol, 10 mol%), Cs_2CO_3 (5.22 g, 16.03 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (1.62 g, 8.016 mmol, 20 mol%) was added 1,4-dioxane (100 mL) followed by allyl acetate (43 mL, 0.401 mol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^oC for 0.5 hr and cooled to ambient temperature. 1,3-Propanediol (3.05 g, 40.08 mmol, 100 mol%) in 1,4-dioxane (100 mL, 0.4 M) was added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^oC for 72 hr. The reaction mixture was filtered through the pad of celite and evaporated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 to 1:1 with 0.1% TEA) provided **5.32** (4.36 g, 27.93 mmol, dr > 30:1) as pale yellow oil in 70% yield.

TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:2). **$[\alpha]_D^{24}$** = –23.5 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.86-5.75 (m, 2H), 5.15-5.09 (m, 4H), 4.01-3.94 (m, 2H), 2.69 (br s, 2H), 2.28-2.23 (m, 4H), 1.62 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.9, 118.3, 68.3,

42.2, 41.7. **FTIR** (neat): υ 3346, 3076, 3005, 2978, 2936, 1827, 1641, 1433, 1335, 1230, 1131, 1071, 1046, 994, 871, 830 cm^{-1}. **HRMS** (CI) Calcd. for $C_9H_{17}O_2$ $(M+H)^+$: 157.1229, Found: 157.1225. **HPLC**: Enantiomeric excess was determined by HPLC analysis of bis-4-nitro-benzoate derivative of the product. (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{minor} = 17.2 min, t_{major} = 40.8 min; ee > 99%.

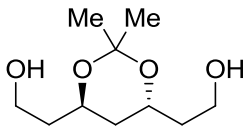
(4*R*,6*R*)-4,6-Diallyl-2,2-dimethyl-1,3-dioxane (5.33)



To a stirred solution of the diol **5.4** (3.5 g, 22.42 mmol, 100 mol%) in DCM (224 mL, 0.1 M) were added 2,2-dimethoxypropane (41 mL, 0.336 mol, 1500 mol%) and pyridinium *p*-toluenesulfonate (0.56 g, 2.242 mmol, 10 mol%) at ambient temperature. The reaction mixture was stirred for 1 hr and quenched with saturated aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with DCM (100 mL × 2). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:50 to 1:15 with 0.1% TEA) to give the acetonide **5.33** (3.99 g, 20.33 mmol) as a colorless oil in 91% yield.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:20). $[\alpha]_D^{24}$ = –56.0 (*c* = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.84-5.73 (m, 2H), 5.10-5.01 (m, 4H), 3.88-3.80 (m, 2H), 2.33-2.25 (m, 2H), 2.21-2.13 (m, 2H), 1.59 (t, *J* = 7.6 Hz, 2H), 1.34 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.7, 117.1, 100.5, 66.4, 40.4, 37.7, 25.1. **FTIR** (neat): υ 3077, 2986, 2937, 1831, 1642, 1431, 1377, 1361, 1172, 1121, 1015, 993, 911, 833, 814 cm^{-1}. **HRMS** (CI) Calcd. for $C_{12}H_{21}O_2$ $[M+H]^+$: 197.1542, Found: 197.1540.

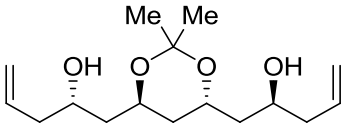
2,2'-((4*R*,6*R*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)diethanol (5.34)



To a stirred solution of the acetonide **5.33** (3.8 g, 19.36 mmol, 100 mol%) in DCM/MeOH (1:1, 130 mL, 0.15 M) was bubbled ozone at −78 ^{o}C until a blue color persisted. The excess ozone was then purged with argon for 5 min. Sodium borohydride (7.3 g, 0.194 mol, 1000 mol%) was added in one portion at – 78 ^{o}C and the resulting solution was slowly warmed to ambient temperature. The mixture was stirred for 24 hr at ambient temperature, and then quenched with H_2O (40 mL). The resulting mixture was concentrated and extracted with DCM (200 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:1 to ethyl acetate:methanol, 20:1 with 0.1% TEA) to give the diol **5.34** (3.42 g, 16.74 mmol) as a colorless oil in 86% yield.

TLC (SiO_2): R_f = 0.28 (ethyl acetate). $[\alpha]_D^{25}$ = –29.0 (*c* = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.08-4.00 (m, 2H), 3.71 (m, 4H), 2.62 (s, 2H), 1.75-1.69 (m, 4H), 1.66 (t, *J* = 7.6 Hz, 2H), 1.34 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 100.8, 66.8, 61.1, 38.3, 37.9, 25.1. **FTIR** (neat): υ 3357, 2986, 2939, 2879, 2359, 1654, 1441, 1416, 1381, 1223, 1164, 1123, 1014, 974, 937, 902, 877 cm^{-1}. **HRMS** (CI) Calcd. for $C_{10}H_{21}O_4$ $[M+H]^+$: 205.1440, Found: 205.1438.

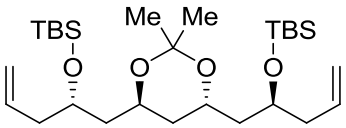
(2*S*,2'*S*)-1,1'-((4*R*,6*R*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)dipent-4-en-2-ol (5.35)



To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (0.58 g, 0.857 mmol, 5 mol%), (*S*)-Cl,MeO-BIPHEP (1.12 g, 1.714 mmol, 10 mol%), Cs_2CO_3 (2.23 g, 6.856 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (0.69 g, 3.428 mmol, 20 mol%) was added THF (43 mL) followed by allyl acetate (1.85 mL, 0.171 mol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and cooled to ambient temperature. The diol **5.34** (3.5 g, 17.14 mmol, 100 mol%) in THF (43 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 110 ^{o}C for 48 hr. The reaction mixture was filtered through the pad of celite and evaporated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 to 1:1 with 0.1% TEA) provided **5.35** (3.46 g, 12.17 mmol, dr > 20:1) as pale yellow oil in 71% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:3). **$[\alpha]_D^{24}$** = –18.0 (*c* = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.85-5.74 (m, 2H), 5.11-5.06 (m, 4H), 4.17-4.09 (m, 2H), 3.86 (br m, 2H), 2.61 (br s, 2H), 2.25-2.15 (m, 4H), 1.66-1.55 (m, 6H), 1.33 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.1, 118.0, 100.9, 67.9, 64.6, 42.3, 41.5, 38.0, 25.0. **FTIR** (neat): υ 3415, 3075, 2985, 2938, 2917, 2850, 1837, 1717, 1640, 1433, 1380, 1222, 1163, 1129, 1081, 1035, 994, 869, 810 cm^{-1}. **HRMS** (CI) Calcd. for $C_{16}H_{29}O_4$ $(M+H)^+$: 285.2066, Found: 285.2066.

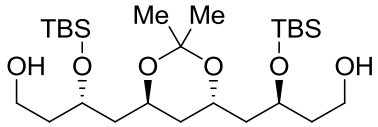
(2*S*,2'*S*)-1,1'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(pent-4-ene-2,1 diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (5.36)



To a stirred solution of the diol **5.35** (0.49 g, 1.723 mmol, 100 mol%) in DMF (3.4 mL, 0.5 M) were added imidazole (0.47 g, 6.892 mmol, 400 mol%) and TBSCl (0.78 g, 5.169 mmol, 300 mol%) at ambient temperature. The reaction mixture was allowed to stir for 48 hr at 45 ^oC, and then quenched with H_2O (5 mL). The reaction mixture was extracted with EtOAc (15 mL × 2). The combined organic extracts were washed with H_2O (3 mL × 2), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:50 to 1:30 with 0.1% TEA) to give **5.36** (0.75 g, 1.464 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.33 (ethyl acetate:hexanes, 1:30). **$[\alpha]_D^{26}$** = +24.0 (*c* = 0.5, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.88-5.77 (m, 2H), 5.11-5.01 (m, 4H), 3.95-3.82 (m, 4H), 2.30-2.16 (m, 4H), 1.67-1.41 (m, 6H), 1.33 (s, 6H), 0.89 (s, 18H), 0.68 (s, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.0, 127.2, 99.9, 68.8, 63.8, 44.1, 42.8, 39.3, 26.2, 25.9, 18.3, -3.7, -4.2. **FTIR** (neat): υ 3078, 2989, 2945, 2929, 2882, 2856, 1641, 1472, 1462, 1434, 1377, 1253, 1223, 1168, 1112, 1061, 1003, 948, 912, 833 cm^{-1}. **HRMS** (CI) Calcd. for $C_{28}H_{57}O_4Si_2$ $[M+H]^+$: 513.3795, Found: 513.3804.

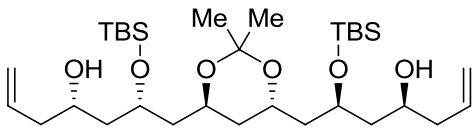
(3*S*,3'*S*)-4,4'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(3-(*tert*-butyldimethylsilyloxy)butan-1-ol) (5.37)



To a stirred solution of **5.36** (0.58 g, 1.132 mmol, 100 mol%) in DCM/MeOH (1:1, 57 mL, 0.02 M) was bubbled ozone at −78 ^{o}C until a blue color persisted. The excess ozone was then purged with argon for 5 min. Sodium borohydride (0.43 g, 11.32 mmol, 1000 mol%) was added in one portion at –78 ^{o}C and the resulting solution was slowly warmed to ambient temperature. The mixture was stirred for 12 hr at ambient temperature, and then quenched with H_2O (5 mL). The resulting solution was then concentrated and extracted with DCM (20 mL × 2). The combined organic extracts was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:3 to 1:1 with 0.1% TEA) to give the diol **5.37** (0.50 g, 0.962 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.24 (ethyl acetate:hexanes, 1:2). **$[\alpha]_D^{26}$** = +28.0 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.01-3.93 (m, 2H), 3.90-3.71 (m, 4H), 3.70-3.65 (m, 2H), 2.40 (br s, 2H), 1.86-1.53 (m, 10H), 1.31 (s, 6H), 0.85 (s, 18H), 0.67 (s, 6H), 0.53 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 100.3, 69.1, 64.1, 59.7, 43.7, 39.4, 39.2, 26.1, 26.0, 25.7, 18.2, -4.1, -4.3. **FTIR** (neat): υ 3398, 2986, 2951, 2992, 2882, 2856, 2242, 1472, 1462, 1429, 1379, 1252, 1223, 1165, 1055, 1005, 938, 909 cm^{-1}. **HRMS** (CI) Calcd. for $C_{26}H_{57}O_6Si_2$ $[M+H]^+$: 521.3694, Found: 521.3691.

(4*S*,4'*S*,6*S*,6'*S*)-7,7'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(6-(*tert*-butyldimethylsilyloxy)hept-1-en-4-ol) (5.38)

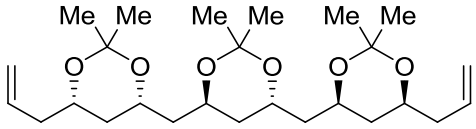


To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (32.2 mg, 0.048 mmol, 5 mol%), (*S*)-Cl,MeO-BIPHEP (62.5 mg, 0.096 mmol, 10 mol%), Cs_2CO_3 (0.125 g, 0.384 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (39 mg, 0.192 mmol,

20 mol%) was added THF (2.4 mL) followed by allyl acetate (1.04 mL, 9.599 mol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and cooled to ambient temperature. The diol **5.37** (0.5 g, 0.960 mmol, 100 mol%) in THF (2.4 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 110 ^{o}C for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:5 to 1:3 with 0.1% TEA) provided **5.38** (0.45 g, 0.749 mmol, dr > 20:1) as pale yellow oil in 78% yield.

TLC (SiO_2): R_f = 0.28 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = +15.0 (*c* = 0.3, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.87-5.76 (m, 2H), 5.12-5.07 (m, 4H), 3.94-3.81 (m, 6H), 2.99 (s, 2H), 2.21 (t, *J* = 6.4 Hz, 4H), 1.85-1.76 (m, 2H), 1.74-1.68 (m, 2H), 1.62-1.53 (m, 6H), 1.32 (s, 6H), 0.88 (s, 18H), 0.79 (s, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.2, 117.7, 100.5, 70.3, 69.0, 64.4, 44.4, 43.9, 42.6, 39.8, 26.1, 25.3, 18.1, -4.0, -4.1. **FTIR** (neat): υ 3432, 3075, 2948, 2928, 2856, 2030, 1720, 1641, 1472, 1462, 1429, 1379, 1359, 1251, 1223, 1165, 1115, 1063, 1003, 938, 912 cm^{-1}. **HRMS** (CI) Calcd. for $C_{32}H_{65}O_6Si_2$ $(M+H)^+$: 601.4320, Found: 601.4318.

(4*S*,4'*S*,6*S*,6'*S*)-6,6'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(methylene)bis(4-allyl-2,2-dimethyl-1,3-dioxane) (5.39)

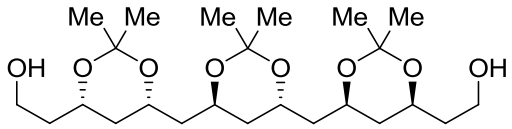


To a stirred solution of **5.38** (0.4 g, 0.666 mmol, 100 mol%) in methanol (6.7 mL, 0.1 M) was added *p*-toluenesulfonic acid monohydrate (12.7 mg, 0.067 mmol, 10 mol%). The reaction mixture was stirred for 1 hr at ambient temperature. TLC analysis showed complete consumption of the starting material. The reaction mixture was diluted with 2,2-dimethoxypropane (8.2 mL, 66.55 mmol, 10000 mol%) and stirred for 1 hr at ambient temperature. After concentrated in vacuo, the residue was diluted with 2,2-dimethoxypropane (4.1 mL, 33.28 mmol, 5000 mol%) and stirred for 1 hr at ambient temperature. The reaction mixture was again concentrated in vacuo. 2,2-Dimethoxypropane (4.1 mL, 33.28 mmol, 5000 mol%) was added and the reaction mixture was stirred for 1 hr at ambient temperature. The reaction mixture was diluted with EtOAc (30 mL) and washed with saturated aq. $NaHCO_3$ (15 mL) and brine (15 mL). The organic

layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:20 to 1:15 with 0.1% TEA) to give **5.39** (0.28 g, 0.619 mmol) as a colorless oil in 93% yield.

TLC (SiO_2): R_f = 0.38 (ethyl acetate:hexanes, 1:10). $[\alpha]_D^{26}$ = +18.5 (*c* = 0.6, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.82-5.72 (m, 2H), 5.08-5.01 (m, 4H), 4.06-3.98 (m, 4H), 3.89-3.83 (m, 2H), 2.31-2.25 (m, 2H), 2.16-2.09 (m, 2H), 1.55-1.46 (m, 8H), 1.40 (s, 6H), 1.36 (s, 6H), 1.30 (s, 6H), 1.16-1.07 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.1, 117.0, 100.4, 98.5, 68.7, 64.9, 62.4, 42.2, 40.8, 39.0, 36.8, 30.2, 24.4, 19.8. **FTIR** (neat): υ 2989, 2941, 2907, 2860, 2239, 2106, 1736, 1642, 1460, 1431, 1373, 1350, 1223, 1199, 1143, 1111, 1024, 981, 939, 911, 881, 812 cm^{-1}. **HRMS** (CI) Calcd. for $C_{26}H_{45}O_6$ $[M+H]^+$: 453.3216, Found: 453.3216.

2,2'-(4*S*,4'*S*,6*S*,6'*S*)-6,6'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(methylene)bis(2,2-dimethyl-1,3-dioxane-6,4-diyl)diethanol (5.3)

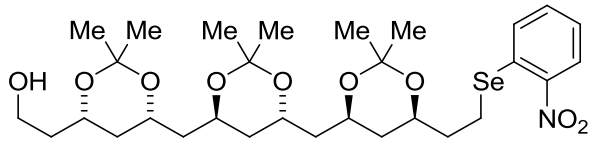


To a stirred solution of **5.39** (0.15 g, 0.331 mmol, 100 mol%) in in DCM/MeOH (1:1, 17 mL, 0.02 M) was bubbled ozone at −78 °C until a blue color persisted. The excess ozone was then purged with argon for 5 min. Sodium borohydride (0.0.125 g, 3.31 mmol, 1000 mol%) was added in one portion at –78 °C and the resulting solution was warmed to ambient temperature slowly. The mixture was stirred for 12 hr at ambient temperature, and then quenched with H_2O (5 mL). The resulting mixture was concentrated and extracted with DCM (20 mL × 2). The combined organic extracts was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:1 to ethyl acetate:methanol 1:20 with 0.1% TEA) to give the diol **5.3** (0.119 g, 0.258 mmol) as a colorless syrup in 78% yield.

TLC (SiO_2): R_f = 0.20 (ethyl acetate:hexanes, 1:1). $[\alpha]_D^{26}$ = +72.5 (*c* = 0.8, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.13-4.02 (m, 6H), 3.81-3.74 (m, 4H), 2.55-2.52 (m, 2H), 1.74-1.70 (m, 4H), 1.58-1.50 (m, 6H), 1.44 (s, 6H), 1.43-1.38 (m, 2H), 1.37 (s, 6H), 1.30 (s, 6H), 1.32-1.24 (m,

2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 100.7, 98.9, 77.5, 69.6, 65.2, 62.6, 60.9, 42.3, 39.1, 38.3, 37.3, 30.5, 24.6, 20.1. **FTIR** (neat): υ 3400, 2990, 2942, 2917, 2882, 1467, 1422, 1380, 1346, 1242, 1222, 1198, 1167, 1137, 1095, 1049, 1010, 936, 910, 875, 824 cm^{-1}. **HRMS** (CI) Calcd. for $C_{24}H_{45}O_8$ $[M+H]^+$: 461.3114, Found: 461.3111.

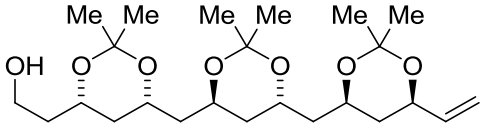
2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-(2-(2-nitrophenylselanyl)ethyl)-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (5.40)



To a stirred solution of the alcohol **5.3** (288 mg, 0.626 mmol, 100 mol%) in THF (3.1 mL, 0.2 M) were added 2-nitrophenyl selenocyanate (156 mg, 0.689 mmol, 110 mol%) and freshly distilled *n*-tributylphosphine (0.17 mL, 0.689 mmol, 110 mol%). The reaction mixture was stirred for 4 hr at ambient temperature and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:15 to 1:10 with 0.1% TEA) to give the selenide **5.40** (202 mg, 0.313 mmol) as a brownish oil in 50% yield and the starting diol **5.3** (61 mg, 0.131 mmol, 21% recovered yield). The recovered diol **3** was subjected to second round of mono-selenylation to give **5.40** (29 mg, 0.066 mmol, 10% yield).

TLC (SiO_2): R_f = 0.20 (ethyl acetate:hexanes, 1:1). **$[\alpha]_D^{26}$** = +2.47 (*c* = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 4.16-3.88 (m, 6H), 3.82-3.68 (m, 2H), 3.10-3.03 (m, 1H), 2.97-2.90 (m, 1H), 2.56 (br s, 1H), 1.95-1.84 (m, 2H), 1.74-1.69 (m, 2H), 1.56-1.46 (m, 6H), 1.43 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.31 (s, 6H), 1.29-1.15 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 146.8, 133.6, 133.5, 129.0, 126.5, 125.3, 100.5, 98.7, 98.6, 77.2, 69.7, 68.4, 64.9, 62.4, 62.3, 61.0, 42.2, 42.1, 38.9, 38.0, 37.0, 35.1, 30.3, 30.2, 24.4, 21.5, 19.9, 19.8. **FTIR** (neat): υ 2945, 1591, 1514, 1381, 1333, 1304, 1248, 1224, 1201, 1166, 1038 cm^{-1}. **HRMS** (CI) Calcd. for $C30H48NO_9Se$ $[M+H]^+$: 646.2494, Found: 646.2497.

2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-vinyl-1,3-dioxan-4-yl)methyl)-2,2 dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (C)

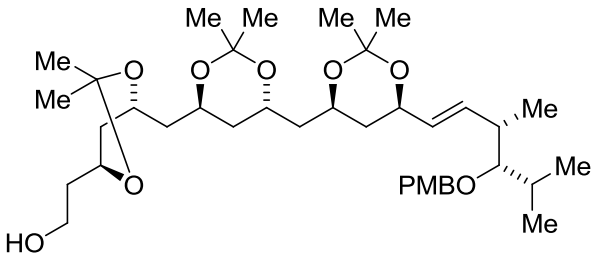


To a stirred solution of the selenide **5.40** (420 mg, 0.651 mmol, 100 mol%) in THF (13 mL, 0.05 M) were added $NaHCO_3$ (164 mg, 1.953 mmol, 300 mol%) and H_2O_2 (0.71 mL, 500 mol%, 30% w/w in H_2O). The reaction mixture was stirred for 24 hr at ambient temperature and extracted with EtOAc. The combined organic extracts was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:3 with 0.1% TEA) to give the allylic ether **C** (251 mg, 0.566 mmol) as a colorless oil in 87% yield.

TLC (SiO_2): R_f = 0.45 (ethyl acetate:hexanes, 1:1). $[\alpha]_D^{26}$ = +11.3 (*c* = 0.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85-5.77 (m, 1H), 5.24 (d, *J* = 17.6 Hz, 1H), 5.11 (d, *J* = 10.4 Hz, 1H), 4.37-4.33 (m, 1H), 4.14-4.01 (m, 5H), 3.78-3.75 (m, 2H), 2.55 (br s, 1H), 1.74-1.70 (m, 2H), 1.61-1.46 (m, 8H), 1.45 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.32 (s, 6H), 1.30-1.23 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.7, 115.3, 100.4, 98.6, 70.3, 69.5, 64.9, 64.7, 62.3, 60.8, 42.1, 42.1, 38.9, 38.0, 37.1, 37.0, 30.3, 30.2, 24.4, 19.8, 19.7. **FTIR** (neat): υ 3491, 2989, 2942, 2915, 1380, 1250, 1224, 1200, 1169, 1142, 1040, 1013, 992, 938, 916, 874, 827, 792 cm^{-1}. **HRMS** (CI) Calcd. for $C_{24}H_{43}O_7$ $[M+H]^+$: 443.3009, Found: 443.3011.

5.5.4 End Game: Combination of Fragments and Synthesis of Roxaticin

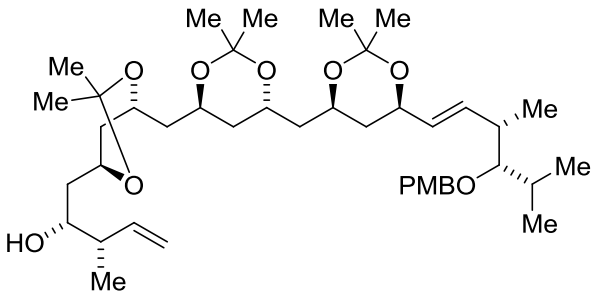
2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (5.41)



To a stirred solution of **C** (245 mg, 0.554 mmol, 100 mol%) and **A** (413 mg, 1.662 mmol, 300 mol%) in DCM (5.5 mL, 0.1 M) was added Hoveyda-Grubbs catalyst 2nd generation (35 mg, 0.055 mmol, 10 mol%). The reaction mixture was stirred for 24 hr at 40 ^{o}C and concentrated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 with 0.1% TEA) provided **5.41** (195 mg, 0.29 mmol) as pale yellow oil in 53% yield.

TLC (SiO_2): R_f = 0.50 (ethyl acetate:hexanes, 1:1). $[\alpha]_D^{26}$ = +11.0 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (m, 2H), 6.86 (dd, *J* = 6.8, 2.0 Hz, 2H), 5.65 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.46 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.47 (s, 2H), 4.36-4.27 (m, 1H), 4.14-4.02 (m, 5H), 3.80 (s, 3H), 3.80-3.74 (m, 2H), 2.96 (m, 1H), 2.54 (br s, 1H), 2.48-2.38 (m, 1H), 1.83-1.78 (m, 1H), 1.74-1.70 (m, 2H), 1.60-1.52 (m, 6H), 1.44 (s, 6H), 1.40 (s, 3H), 1.37 (s, 3H), 1.32 (s, 6H), 1.30-1.21 (m, 4H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.9, 135.7, 131.1, 129.8, 129.2, 113.6, 100.4, 98.5, 98.4, 88.4, 74.7, 70.3, 69.3, 64.9, 64.7, 62.3, 60.6, 55.1, 42.1, 39.4, 38.9, 38.2, 38.0, 37.5, 37.0, 30.9, 30.2, 24.3, 20.2, 19.7, 17.7, 15.2. **FTIR** (neat): υ 2997, 1979, 1674, 1514, 1382, 1215, 1037, 935, 746, 696, 667 cm^{-1}. **HRMS** (CI) Calcd. for $C_{38}H_{61}O_9$ $[M-H]^+$: 661.4316, Found: 661.4323.

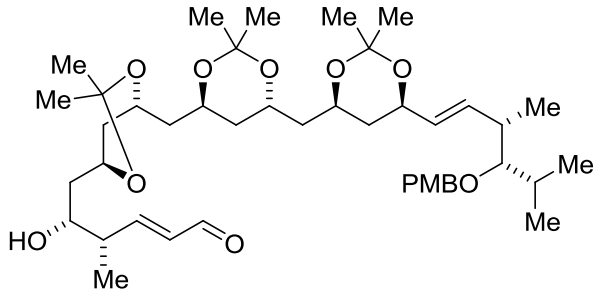
(2*R*,3*S*)-1-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-methylpent-4-en-2-ol (5.42)



An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with alcohol **5.41** (133 mg, 0.2 mmol, 100 mol%), ***(S)*-II** (20.7 mg, 0.02 mmol, 10 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 □L, 1.0 mmol, 500 mol%) and crotyl acetate (68 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:7 with 0.1% TEA) provided **5.42** (121.9 mg, 0.17 mmol) as a yellow oil in 85% yield (14:1 dr).

TLC (SiO_2): R_f = 0.65 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = +98.0 (*c* = 1.0, CH_2Cl_2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.86-5.77 (m, 1H), 5.65 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.46 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.07 (s, 1H), 5.03 (d, *J* = 6.0 Hz, 1H), 4.47 (s, 2H), 4.34-4.26 (m, 1H), 4.14-3.98 (m, 5H), 3.79 (s, 3H), 3.72-3.66 (m, 1H), 3.45 (s, 1H), 2.97-2.94 (m, 1H), 2.44-2.39 (m, 1H), 2.24-2.20 (m, 1H), 1.83-1.78 (m, 1H), 1.56-1.46 (m, 8H), 1.45 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.32 (s, 6H), 1.30-1.20 (m, 4H), 1.05 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 158.9, 140.4, 135.7, 131.1, 129.8, 129.2, 115.0, 113.6, 100.3, 98.6, 98.5, 88.4, 74.7, 74.6, 70.4, 70.2, 64.9, 64.7, 62.3, 62.2, 55.1, 43.8, 42.1, 42.0, 39.7, 39.4, 38.9, 37.5, 37.4, 30.9, 30.2, 30.1, 24.3, 20.2, 19.8, 19.8, 17.7, 15.4, 15.2. **FTIR** (neat): υ 3502, 2987, 2943, 1940, 1737, 1613, 1514, 1461, 1431, 1380, 1301, 1247, 1224, 1200, 1168, 1127, 1087, 1037, 980, 936, 913, 874, 823, 702 cm^{-1}. **HRMS** (CI) Calcd. for $C_{42}H_{67}O_9$ $[M-H]^+$: 715.4786, Found: 715.4786.

(4*S*,5*R*,*E*)-5-hydroxy-6-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methylhex-2-enal (5.43)

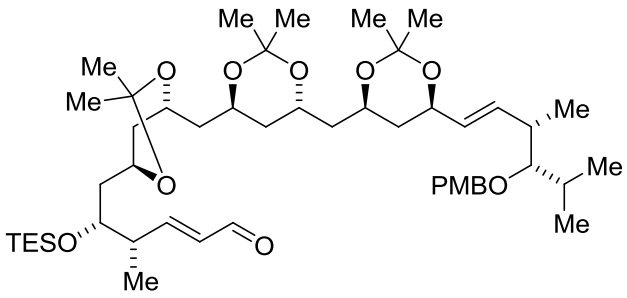


To a stirred solution of **5.42** (122 mg, 0.170 mmol, 100 mol%) and acrolein (48 mg, 0.85 mmol, 500 mol%) in DCE (1.7 mL, 0.1 M) was added Hoveyda-Grubbs catalyst 2nd generation (8.0 mg, 0.013 mmol, 7.5 mol%). The reaction mixture was stirred for 24 hr at 60 ^{o}C. Acrolein (48 mg, 0.85 mmol, 500 mol%) and Hoveyda-Grubbs catalyst 2nd generation (8.0 mg, 0.013 mmol, 7.5 mol%) were added and the reaction mixture was stirred for 24 hr at 60 ^{o}C. The reaction mixture was concentrated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 with 0.1% TEA) provided the starting material **5.42** (37 mg, 0.051mmol, 30% recovered yield) and the product **5.43** (66 mg, 0.09 mmol, 52% yield, 74% BRSM) as a pale yellow oil.

TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:3). **$[\alpha]_D^{26}$** = +70.0 (*c* = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.53 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.94 (dd, *J* = 15.6, 8.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.12 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.65 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.45 (dd, *J* = 15.2, 6.0 Hz, 1H), 4.47 (s, 2H), 4.32-4.27 (m, 1H), 4.12-3.98 (m, 5H), 3.86-3.80 (m, 2H), 3.79 (s, 3H), 2.97-2.93 (m, 1H), 2.49-2.40 (m, 2H), 1.83-1.77 (m, 1H), 1.56-1.46 (m, 8H), 1.46 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.28-1.19 (m, 4H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.0, 160.0, 158.9, 135.7, 132.9, 131.1, 129.8, 129.2, 113.6, 100.4, 98.8, 98.5, 88.4, 74.8, 74.7, 70.8, 70.3, 64.8, 64.7, 62.3, 62.2, 55.2, 43.2, 42.1, 41.9, 40.4, 39.4, 38.8, 37.5, 37.4, 30.9, 30.2, 30.1, 24.3, 20.2, 19.8, 19.7, 17.7, 15.6, 15.2. **FTIR** (neat): υ 3508,

2987, 2940, 1690,1613, 1514, 1459, 1380, 1301, 1247, 1224, 1200, 1168, 1127, 1085, 1036, 977, 936, 874, 821, 732 cm^{-1}. **HRMS** (CI) Calcd. for $C_{43}H_{67}O_{10}$ $[M-H]^+$: 743.4734, Found: 743.4738

3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methyl-5-(triethylsilyloxy)hex-2-enal (5.43a)

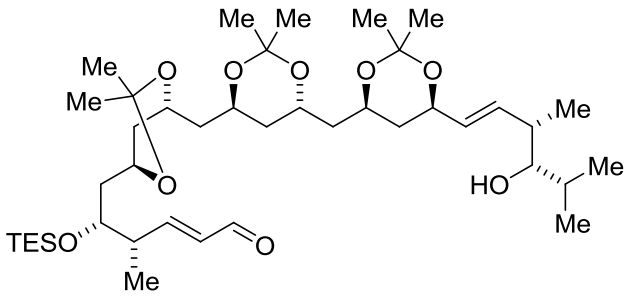


To a stirred solution of **5.43** (37 mg, 0.05 mmol, 100 mol%) in DCM (0.5 mL, 0.1 M) were added 2,6-lutidine (23 µL, 0.2 mmol, 400 mol%) and TESOTf (23 µL, 0.1 mmol, 200 mol%) at -78 ^oC. The reaction mixture was stirred for 2 hr at -78 ^oC, and then quenched with saturated aq. $NaHCO_3$ (2 mL). The reaction mixture was extracted with DCM. The combined organic extracts wase washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:20 to 1:10 with 0.1% TEA) to give **5.43a** (38 mg, 0.044 mmol) as a yellow oil in 87% yield.

TLC (SiO_2): R_f = 0.60 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = +29.0 (*c* = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.51 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.90-6.85 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.09 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.65 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.45 (dd, *J* = 15.2, 5.6 Hz, 1H), 4.47 (s, 2H), 4.34-4.26 (m, 1H), 4.10-3.96 (m, 4H), 3.95-3.88 (m, 1H), 3.88-3.82 (m, 1H), 3.79 (s, 3H), 2.97-2.94 (m, 1H), 2.66-2.58 (m, 1H), 2.46-2.38 (m, 1H), 1.84-1.76 (m, 1H), 1.56-1.46 (m, 8H), 1.44 (s, 3H), 1.39 (s, 6H), 1.34 (s, 3H), 1.32 (s, 6H), 1.28-1.21 (m, 4H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.98-0.92 (m, 15H), 0.63 (q, *J* = 7.6 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 193.9, 160.4, 158.9, 135.6, 132.9, 131.1, 129.8, 129.1, 113.5, 100.3, 98.4, 98.2, 88.4, 74.7, 71.5, 70.2, 65.6, 64.9, 64.7, 62.3, 55.1, 42.1, 42.0, 41.9, 41.8, 39.4, 38.9, 37.6, 37.5,30.8, 30.2, 30.1, 24.3, 20.2, 19.7, 19.6, 17.7, 15.9, 15.1, 6.8, 5.0. **FTIR** (neat): υ 2987, 2950, 2912, 2876, 1693, 1613, 1514, 1460, 1379, 1301, 1246, 1224, 1199, 1169,

1128, 1083, 1034, 981, 938, 873, 854, 821, 781, 740, 726 cm^{-1}. **HRMS** (CI) Calcd. for $C_{49}H_{81}O_{10}Si_1$ $[M-H]^+$: 857.5599, Found: 857.5602.

(4*S*,5*R*,*E*)-6-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-hydroxy-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methyl-5-(triethylsilyloxy)hex-2-enal (5.44)

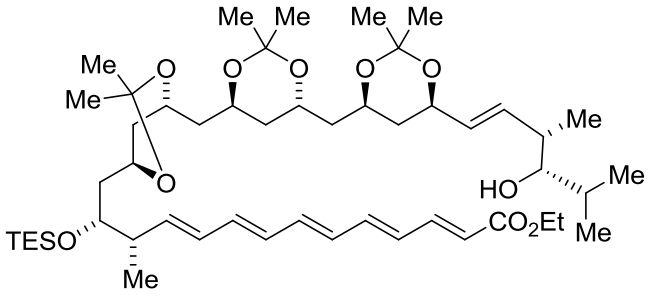


To a stirred solution of **5.43a** (38 mg, 0.044 mmol, 100 mol%) in DCM/H_2O (1.4 mL/0.07 mL, 0.03M) was added DDQ (13 mg, 0.057 mmol, 130 mol%) at 0 ^oC. The reaction mixture was stirred for 2 hr at 0 ^oC, and then quenched with saturated aq. $NaHCO_3$ (0.5 mL). The reaction mixture was extracted with DCM. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:7 to 1:5 with 0.1% TEA) to give **5.44** (28 mg, 0.037 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = +78.0 (*c* = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.50 (d, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 15.6, 8.0 Hz, 1H), 6.09 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.62 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.48 (dd, *J* = 15.6, 6.0 Hz, 1H), 4.34-4.31 (m, 1H), 4.10-3.96 (m, 4H), 3.95-3.87 (m, 1H), 3.87-3.81 (m, 1H), 3.16-3.13 (m, 1H), 2.66-2.57 (m, 1H), 2.36-2.31 (m, 1H), 1.74-1.67 (m, 1H), 1.59-1.45 (m, 8H), 1.44 (s, 3H), 1.39 (s, 6H), 1.34 (s, 3H), 1.32 (s, 6H), 1.28-1.21 (m, 4H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98-0.89 (m, 15H), 0.60 (q, *J* = 8.0 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.0, 160.6, 134.8, 132.9, 130.9, 100.4, 98.5, 98.3, 79.5, 71.6, 70.2, 65.7, 64.9, 64.7, 62.3, 42.2, 42.1, 41.8, 39.2, 38.9, 37.6, 30.4, 30.2, 30.1, 24.3, 19.7, 19.6, 17.0, 15.9, 13.8, 6.8, 5.0. **FTIR** (neat): υ 3515, 2987, 2950, 2876, 1692, 1634, 1459, 1379, 1224, 1199, 1168, 1142, 1084, 1021, 1006, 981, 938,

913, 874, 855, 816, 781, 731 cm^{-1}. **HRMS** (CI) Calcd. for $C_{41}H_{73}O_9Si_1$ $[M-H]^+$: 737.5024, Found: 737.5012.

(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*)-ethyl 14-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-hydroxy-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-12-methyl-13-(triethylsilyloxy)tetradeca-2,4,6,8,10-pentaenoate (5.45)



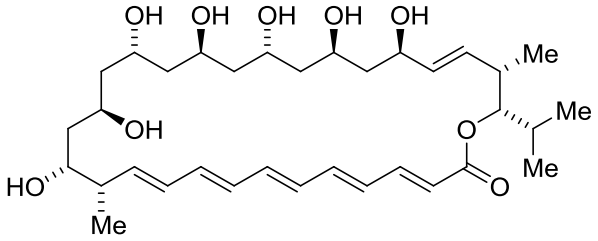
This entire experimental procedure was performed in the dark.

To a stirred solution of $EtO_2C(CH=CH)_3CH_2PO(OEt)_2$ **A** (34 mg, 0.111 mmol, 300 mol%) in THF (1.11 mL. 0.1 M) was added LHMDS (0.11 mL, 1.0 M in THF, 0.111 mmol, 300 mol%) at -78 ^oC. The reaction mixture was stirred for 30 min at -78 ^oC, and a solution of **5.44** (28 mg, 0.037 mmol, 100 mol%) in THF (0.37 mL. 0.1 M) was added slowly -78 ^oC. The resulting solution was stirred for 30 min at -78 ^oC and gradually warmed to ambient temperature. The reaction mixture was stirred for an additional 8 hr, and then quenched with saturated aq. NH_4Cl. The resulting solution was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:7 to 1:5 with 0.1% TEA) to give **5.45** (59 mg, 0.067 mmol) as a yellow oil in 61% yield.

TLC (SiO_2): R_f = 0.55 (ethyl acetate:hexanes, 1:3). $[\alpha]_D^{26}$ = -11.0 (*c* = 1.0, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.59 (dd, *J* = 14.4, 11.2 Hz, 1H), 6.42 (dd, *J* = 14.0, 10.4 Hz, 1H), 6.34-6.25 (m, 3H), 6.20 (dd, *J* = 14.8, 10.4 Hz, 1H), 6.07 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.85 (d, *J* = 14.8 Hz, 1H), 5.74 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.62 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.49 (dd, *J* = 14.8, 5.2 Hz, 1H), 4.28-4.36 (m, 1H), 4.20 (q, *J* =7.2 Hz, 2H), 4.10-

3.96 (m, 4H), 3.96-3.86 (m, 1H), 3.76-3.68 (m, 1H), 3.20-3.12 (m, 1H), 2.37-2.33 (m, 2H), 1.74-1.67 (m, 1H), 1.56-1.44 (m, 8H), 1.43 (s, 3H), 1.38 (s, 6H), 1.33 (s, 3H), 1.31 (s, 6H), 1.28-1.21 (m, 4H), 1.03-0.87 (m, 24H), 0.59 (q, J = 8.0 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.1, 144.4, 140.8, 139.0, 137.4, 135.9, 134.8, 131.2, 131.0, 130.6, 130.5, 129.5, 120.3, 100.4, 98.6, 98.3, 79.6, 71.9, 70.2, 66.2, 64.9, 64.7, 62.4, 62.3, 60.2, 42.6, 42.3, 42.1, 41.1, 39.2, 38.9, 37.6, 30.5, 30.2, 30.1, 24.4, 19.8, 19.7,19.6, 17.1, 15.7, 14.3, 13.7, 6.9, 5.1. **FTIR** (neat): υ 3510, 2952, 2875, 1708, 1622, 1578, 1459, 1379, 1300, 1248, 1224, 1199, 1168, 1128, 1007, 937, 912, 874, 817, 737 cm^{-1}. **HRMS** (ESI) Calcd. for $C_{51}H_{86}O_{10}Si$ $[M+Na]^+$: 909.5882, Found: 909.5880.

(3*E*,5*E*,7*E*,9*E*,11*E*,13*S*,14*R*,16*R*,18*R*,20*S*,22*S*,24*R*,26*R*,27*E*,29*S*,30*S*)-14,16,18,20,22,24,26-heptahydroxy-30-isopropyl-13,29-dimethyloxacyclotriaconta-3,5,7,9,11,27-hexaen-2-one
(+)-Roxaticin



This entire experimental procedure was performed in the dark.

To a stirred solution of **5.45** (59 mg, 0.067 mmol, 100 mol%) in 4:1:1 THF/MeOH/H_2O (3.35 mL, 0.02 M) was added LiOH (0.34 mL, 1.0 M in H_2O, 0.335 mmol, 500 mol%) at ambient temperature. The reaction mixture was stirred for 6 hr at ambient temperature, and diluted with saturated aq. NH_4Cl. The resulting solution was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting seco-acid was employed directly in the next reaction.

To a stirred solution of the seco-acid in THF (3.35 mL, 0.02 M) were added Et_3N (19 µL, 0.134 mmol, 200 mol%) and 2,4,6-trichlrobenzoyl chloride (16 µL, 0.101 mmol, 150 mol%). The reaction mixture was stirred for 3 hr at ambient temperature, filtered through the pad of celite and diluted with toluene (10 mL). This solution was added over a period of 8 hr using a syringe pump to a solution of 4-dimethylaminopyridine (327 mg, 2.68 mmol, 4000 mol%) in toluene

(133 mL, 0.02 M) at 50 ^{o}C. The reaction mixture was stirred for an additional 4 hr, and toluene was removed under reduced pressure. The cloudy oil was diluted in 1:1 hexanes/ethyl acetate, filtered through a silica plug over a pad of celite and washed with 1:1 hexanes/ethyl acetate, then concentrated under reduced pressure to afford a bright yellow oil. The resulting oil was used directly in the next reaction.

A solution of protected crude roxaticin in MeOH (5 mL) was treated with Dowex 50Wx8 acidic resin (100 mg). After being stirred for 4 hr, the mixture was filtered and concentrated in vacuo. Purification by preparative reverse-phase thin-layer chromatography (RP-18, 100x100x0.25 mm, two plate, 10% H_2O/MeOH) gave **(+)-roxaticin** (12.6 mg, 0.0208 mmol, 31% yield) as a yellow solid.

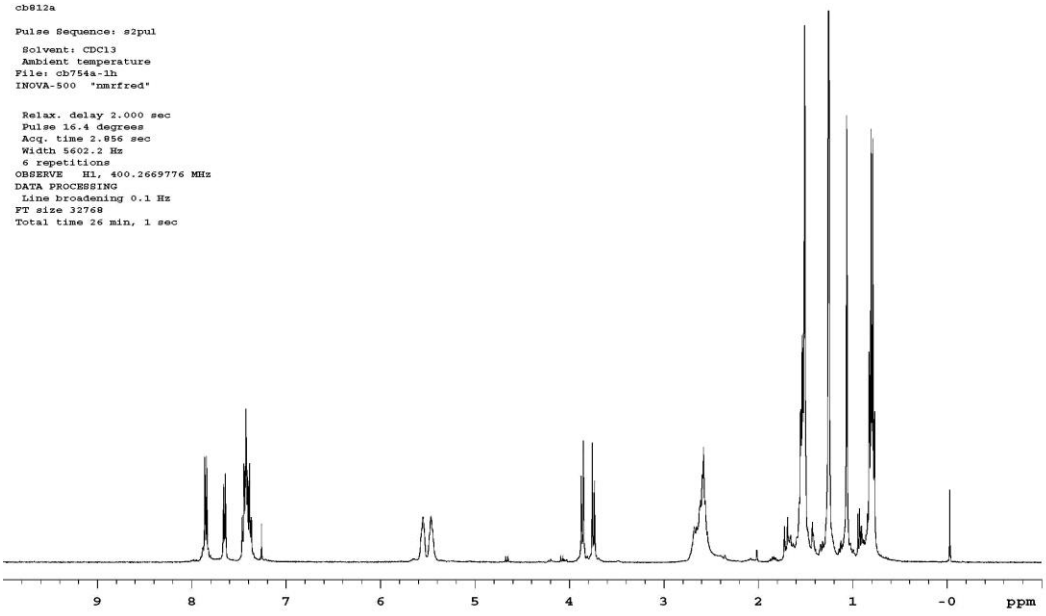
$[\alpha]_D^{26}$ = +11.3 (*c* = 0.17, dioxane). **^{1}H NMR** (400 MHz, DMSO- d_6): δ 7.11 (dd, *J* = 15.6, 11.6 Hz, 1H), 6.69 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.47 (dd, *J* = 14.4, 11.2 Hz, 1H), 6.42-6.26 (m, 4H), 6.10 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.88 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.82 (d, *J* = 15.2 Hz, 1H), 5.54 (dd, *J* = 15.6, 5.1 Hz, 1H), 5.34 (dd, *J* = 16.0, 3.6 Hz, 1H), 5.01 (s, 1H), 4.65 (dd, *J* = 7.2, 2.5 Hz, 1H), 4.59 (d, *J* = 3.6 Hz, 1H), 4.36 (d, *J* = 4.0 Hz, 1H), 4.20 (d, *J* = 5.4 Hz, 1H), 4.15 (m, 1H), 4.12 (d, *J* = 5.0 Hz, 1H), 3.93 (d, *J* = 5.8 Hz, 1H), 3.84 (m, 1H), 3.98-3.72 (m, 5H), 3.42 (m, 1H), 2.55 (m, 2H), 1.86 (m 1H), 1.48 (m, 2H), 1.40-0.99 (m, 10H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.1, 144.6, 141.1,139.2, 137.6, 135.7, 133.1, 131.0, 130.4, 129.4, 129.1, 128.7, 120.2, 79.3, 71.0, 69.8, 67.7, 64.9, 64.3, 62.9, 62.4, 47.3, 46.7, 46.6, 44.4, 44.3, 42.6, 40.9, 35.7, 28.8, 19.7, 18.7, 13.7, 10.8. **FTIR** (neat): υ 3410, 1708, 1612, 1588, 1379, 1304, 1268, 1138, 1007, 933, 910, 872, 737 cm^{-1}. **HRMS** (ESI) Calcd. for $C_{41}H_{73}O_9Si_1$ $[M+Na]^+$: 629.3600, Found: 629.3663.

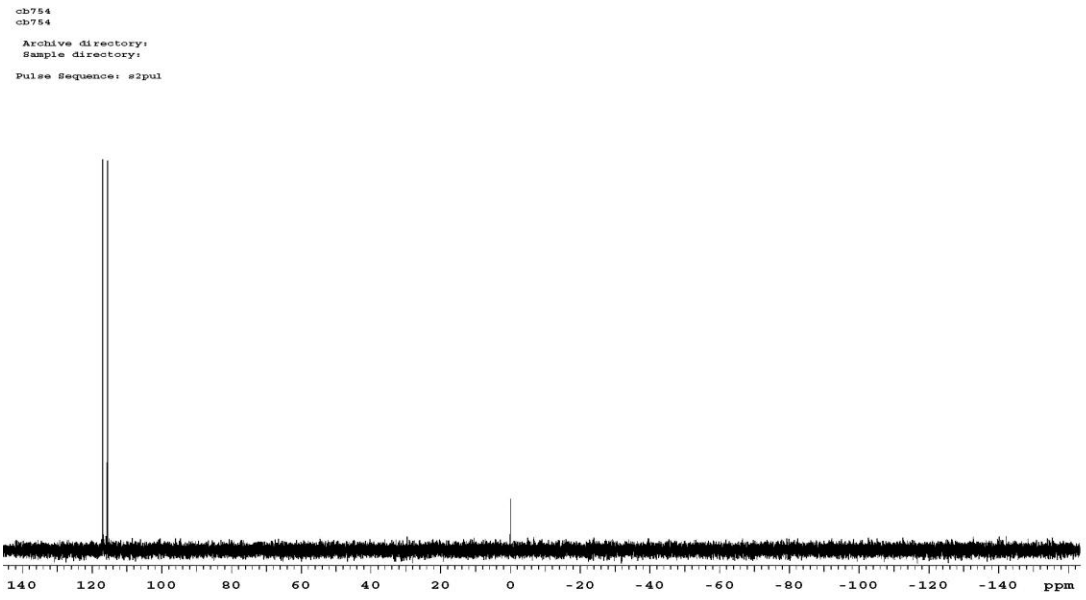
Appendix I: NMR Spectra of New Compounds

Chapter 2

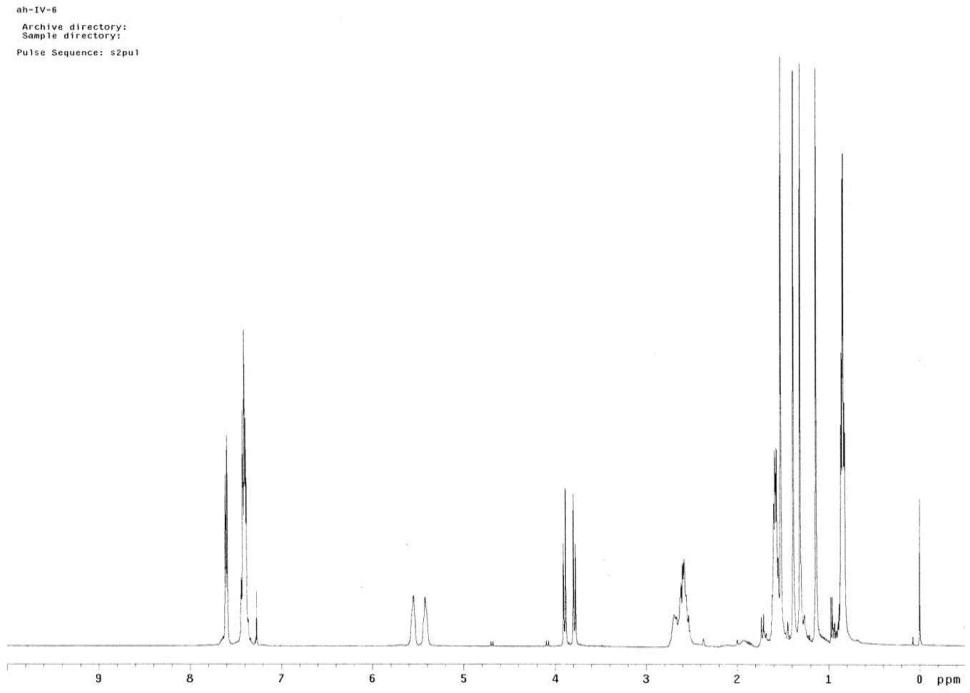
I Experimental Procedures for Catalyst Formation

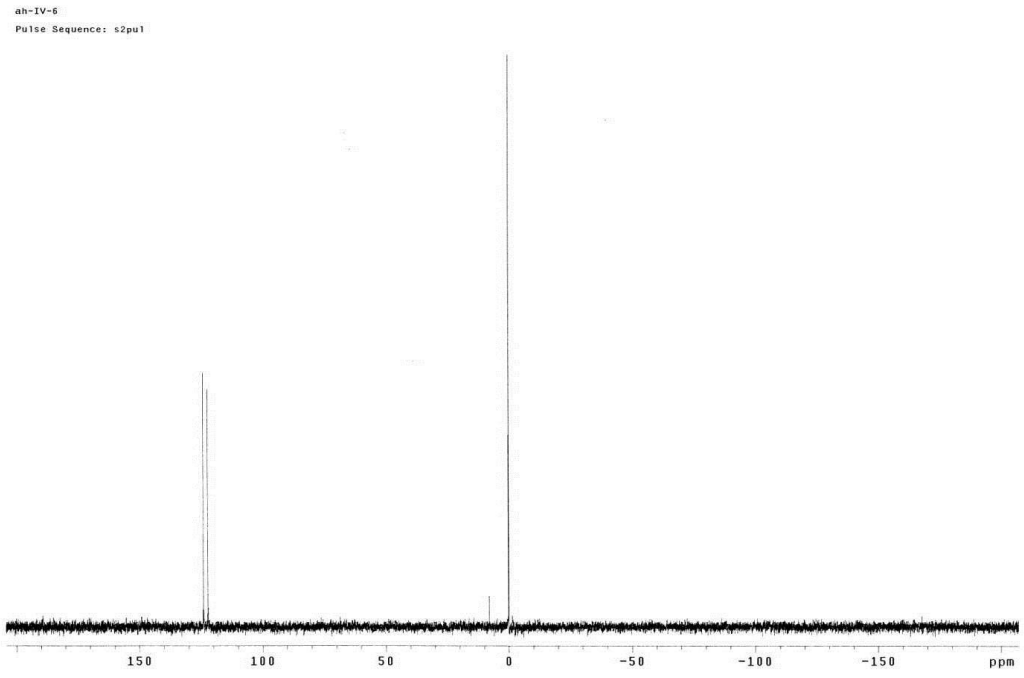
$[Rh(cod)(AP\text{-}I)_2]OTf$





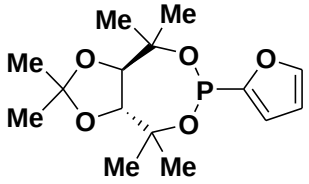
[Rh(cod)(AP-IV)$_2$]OTf

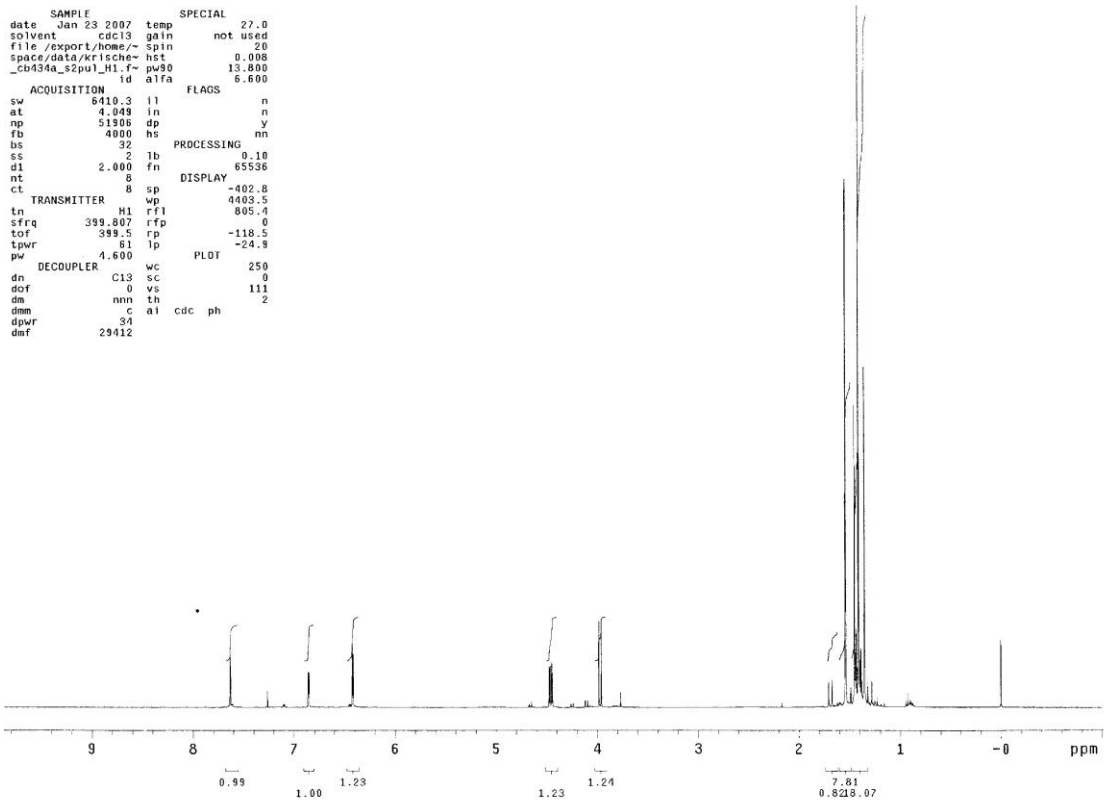


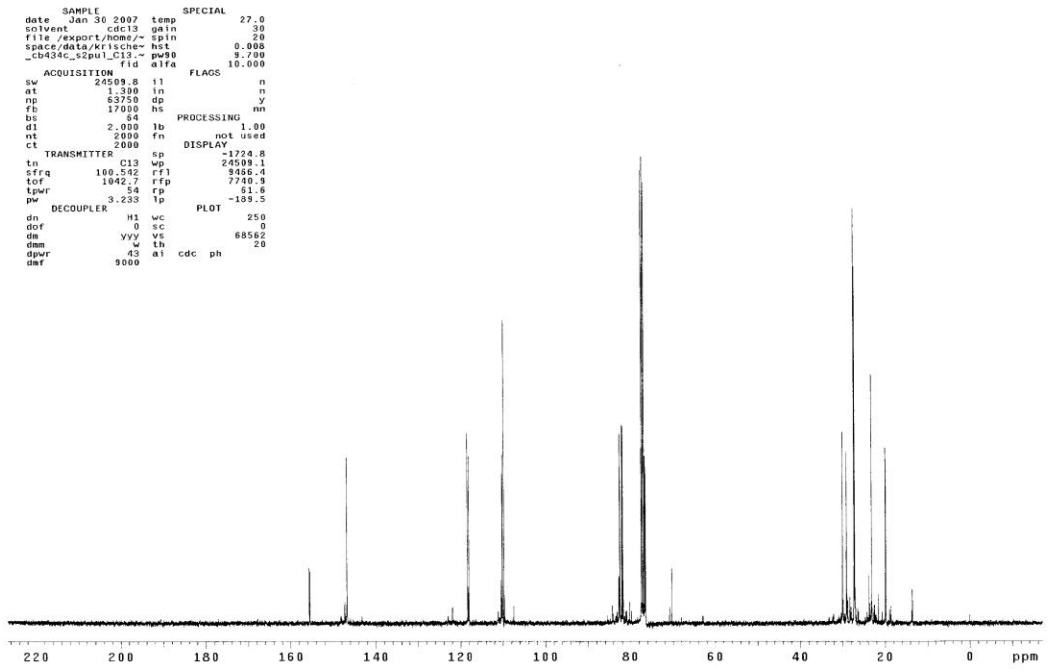


II Spectroscopic Data Chiral Ligands

(3a*R*,8a*R*)-6-(furan-2-yl)-tetrahydro-2,2,4,4,8,8-hexamethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.57







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cb434a

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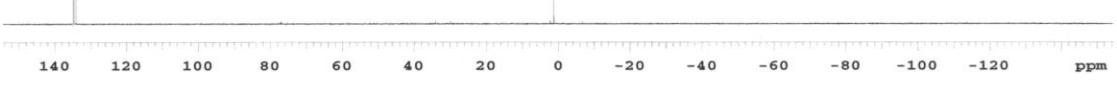
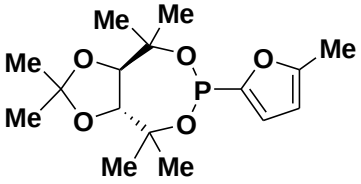
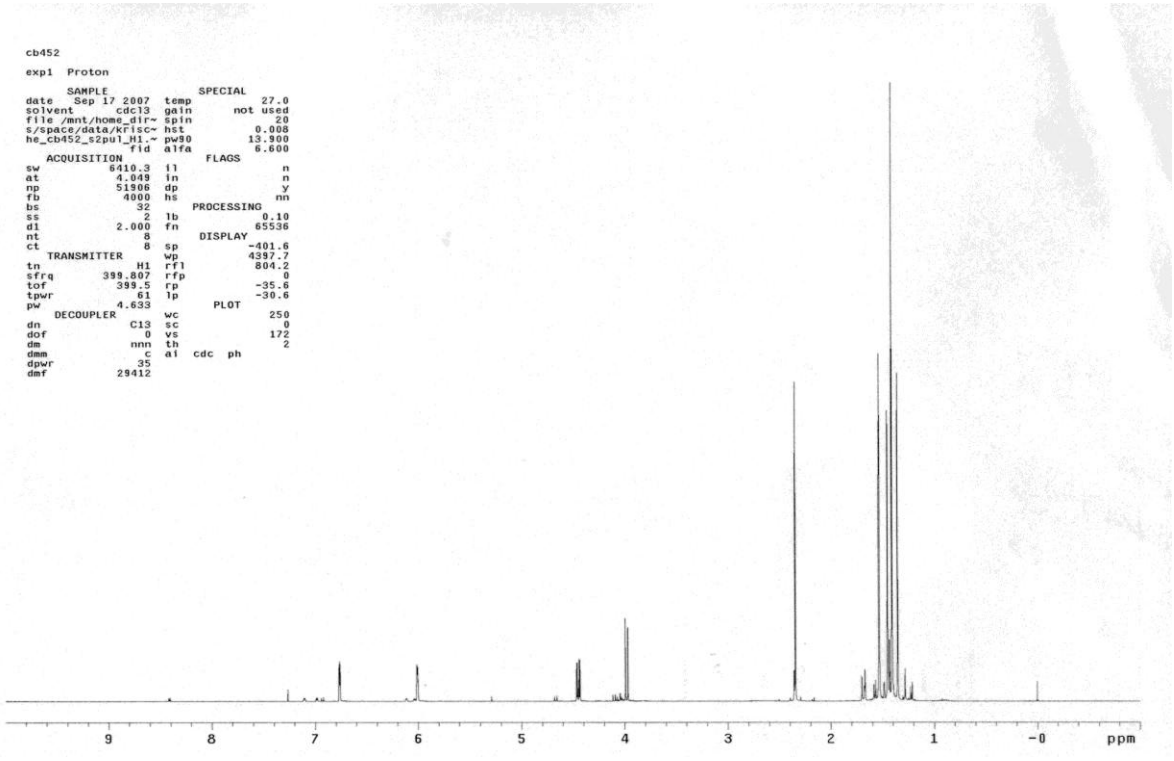


(3a*R*,8a*R*)-tetrahydro-2,2,4,4,8,8-hexamethyl-6-(5-methylfuran-2-yl)-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine], 2.56





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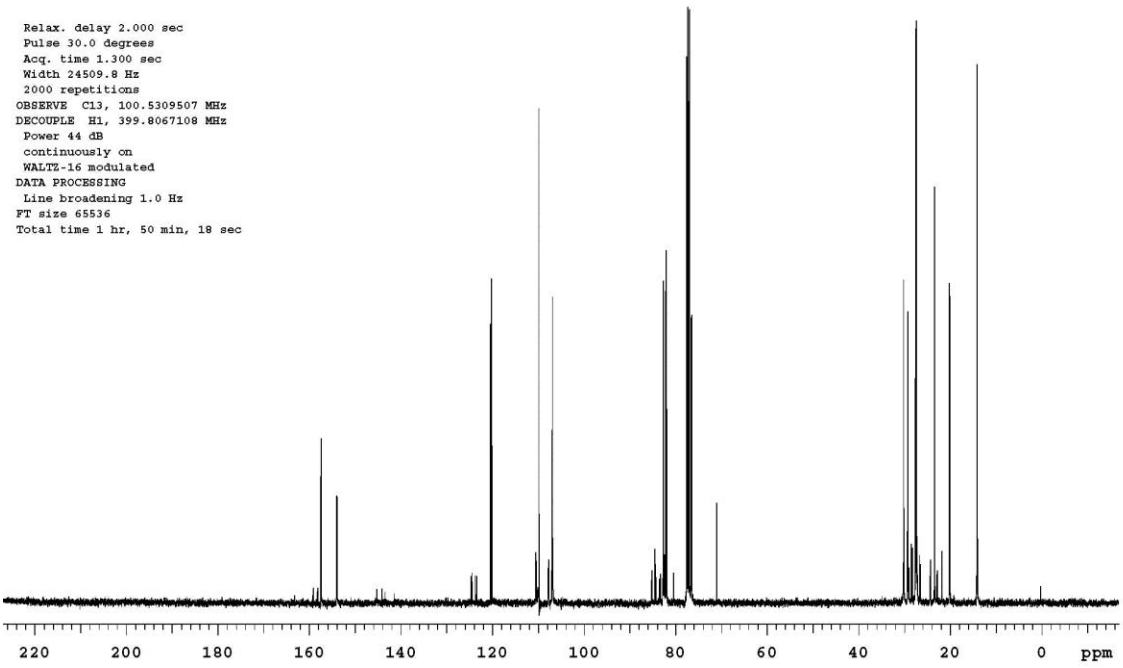

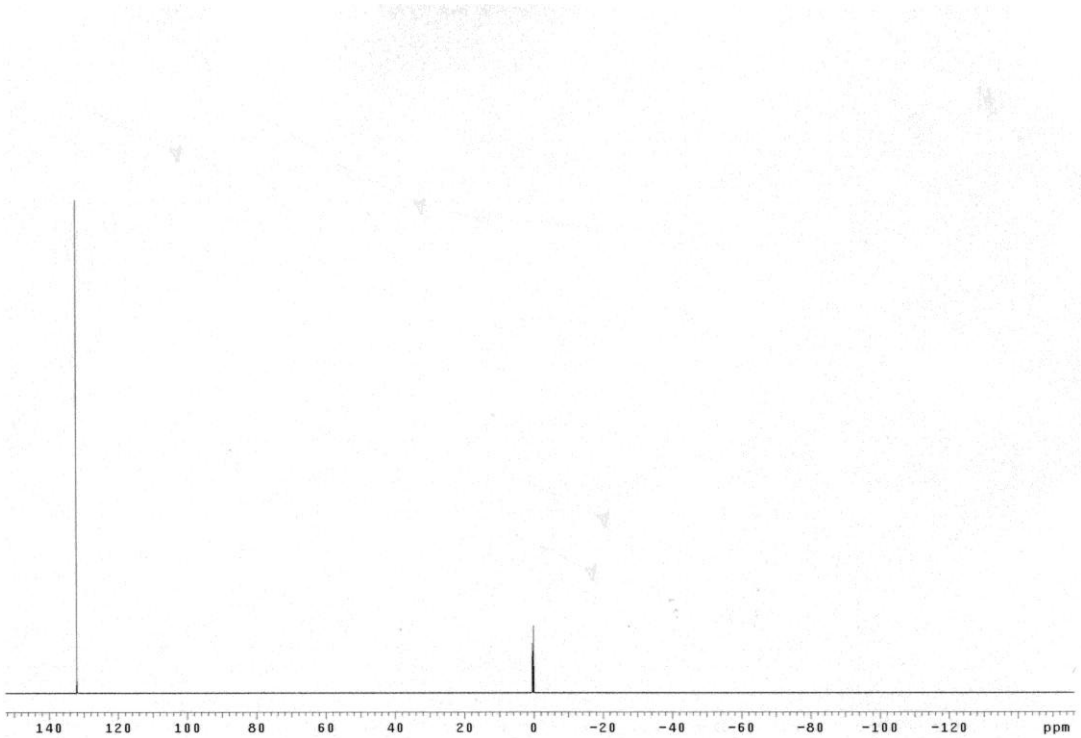

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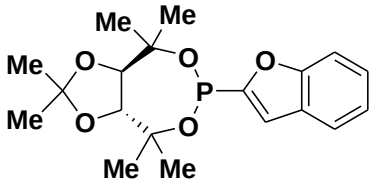

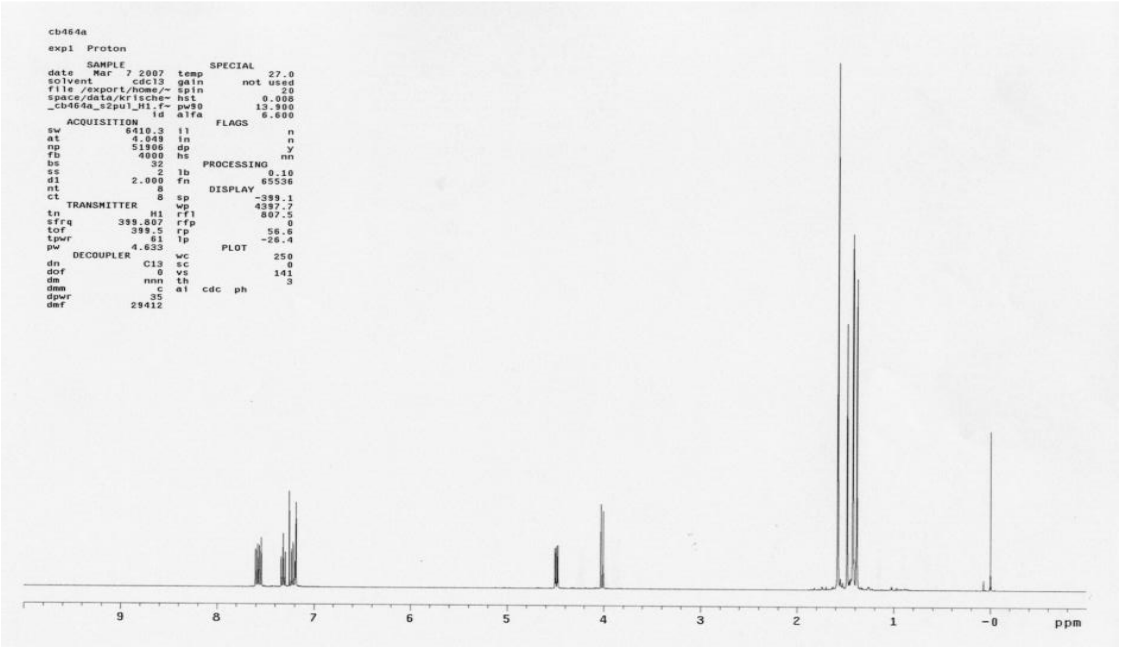

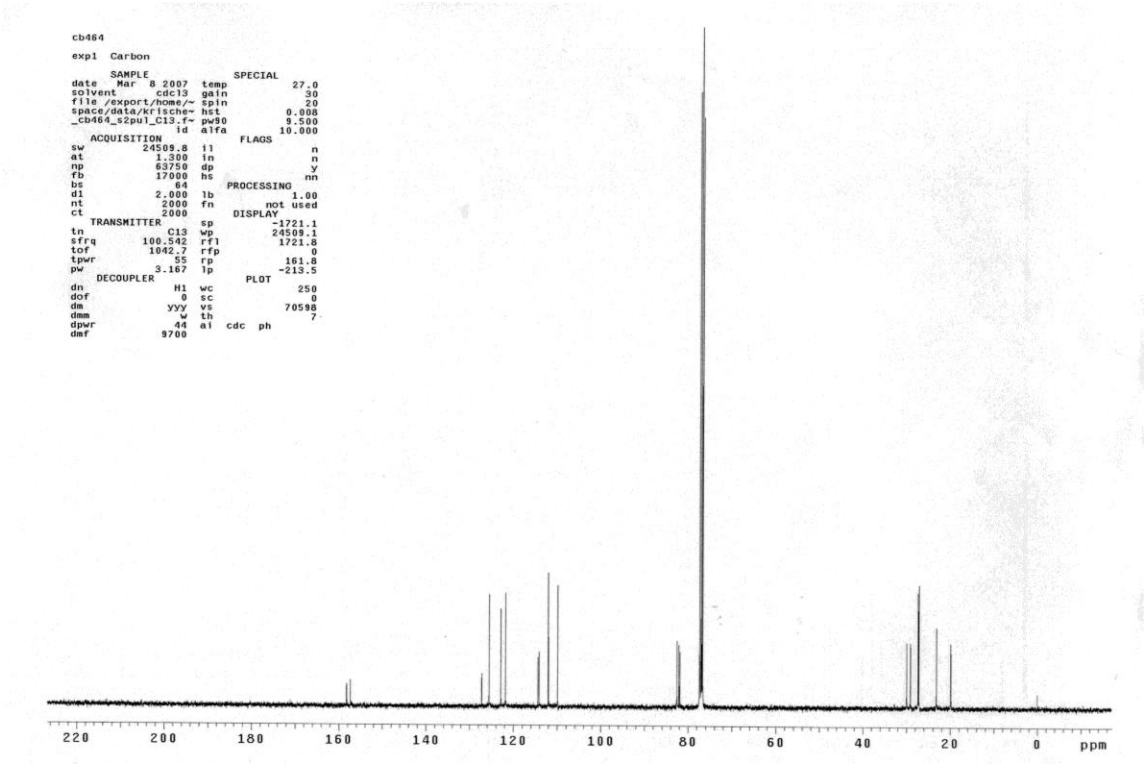
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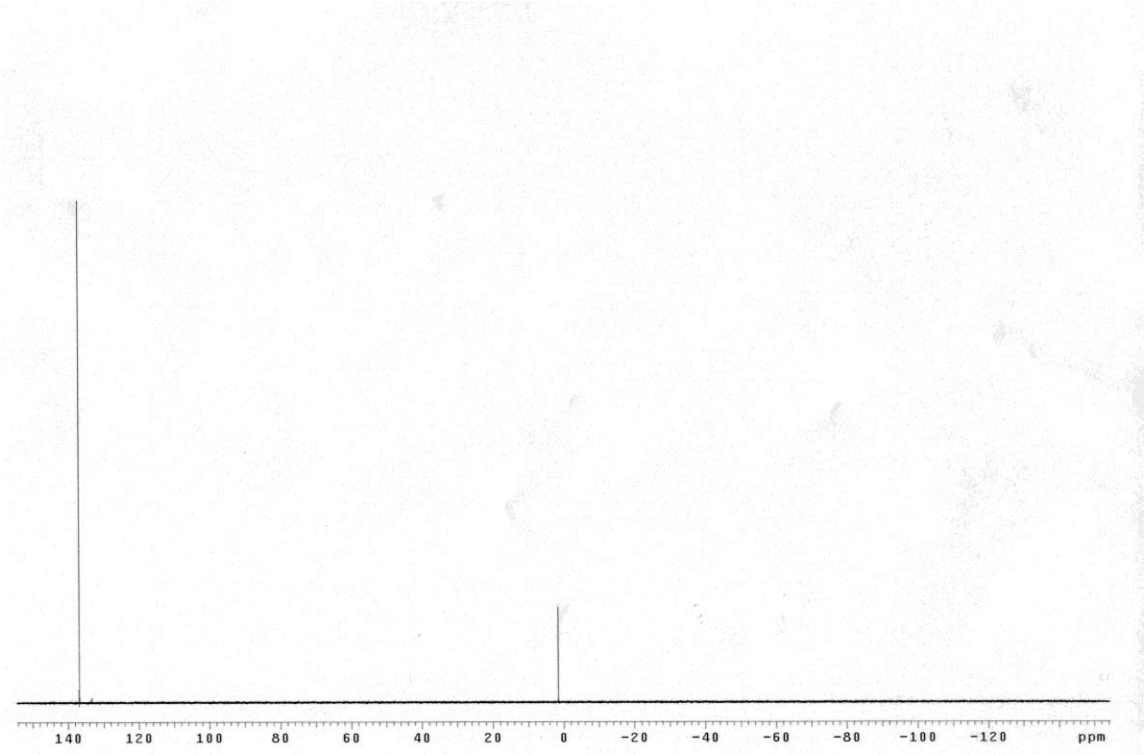
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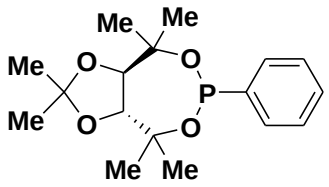
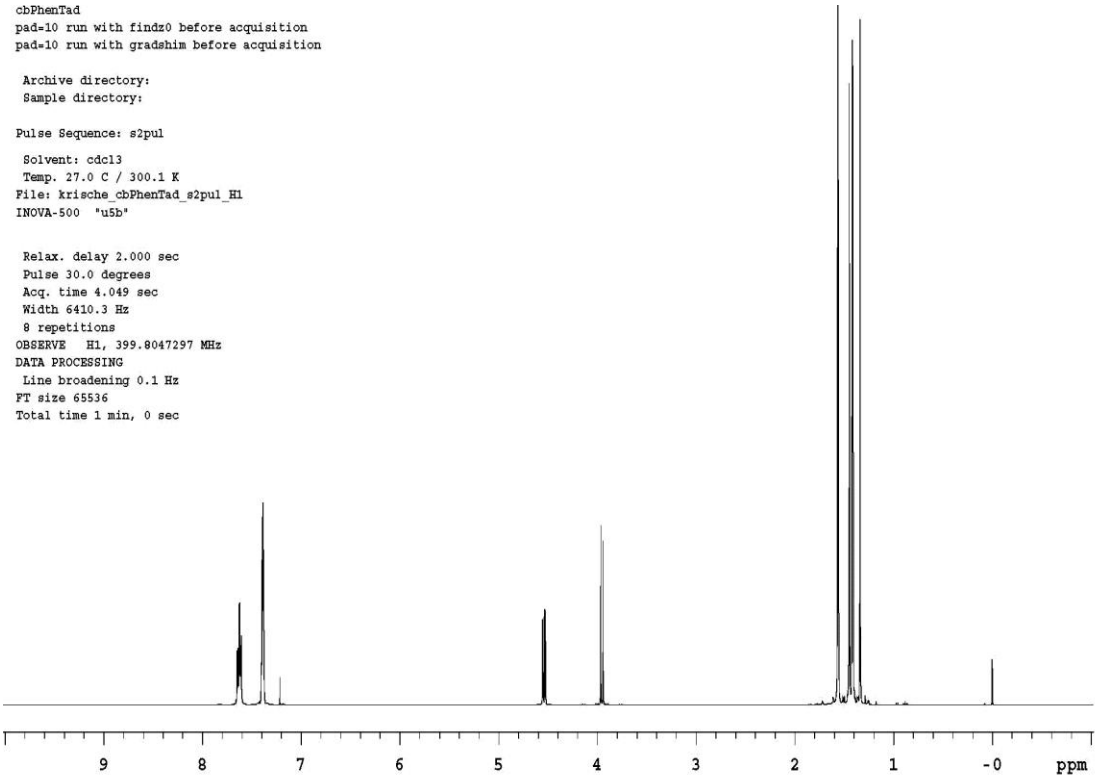
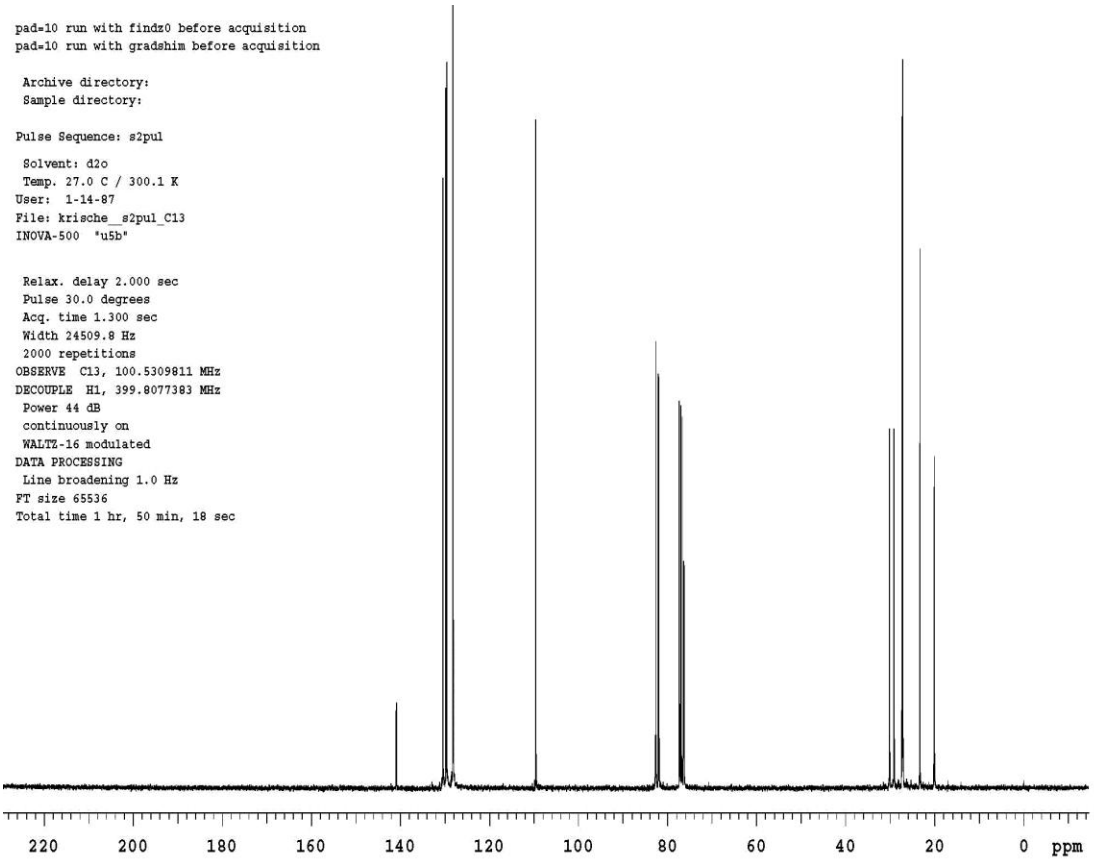
(3a*R*,8a*R*)-tetrahydro-2,2,4,4,8,8-hexamethyl-6-phenyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.60



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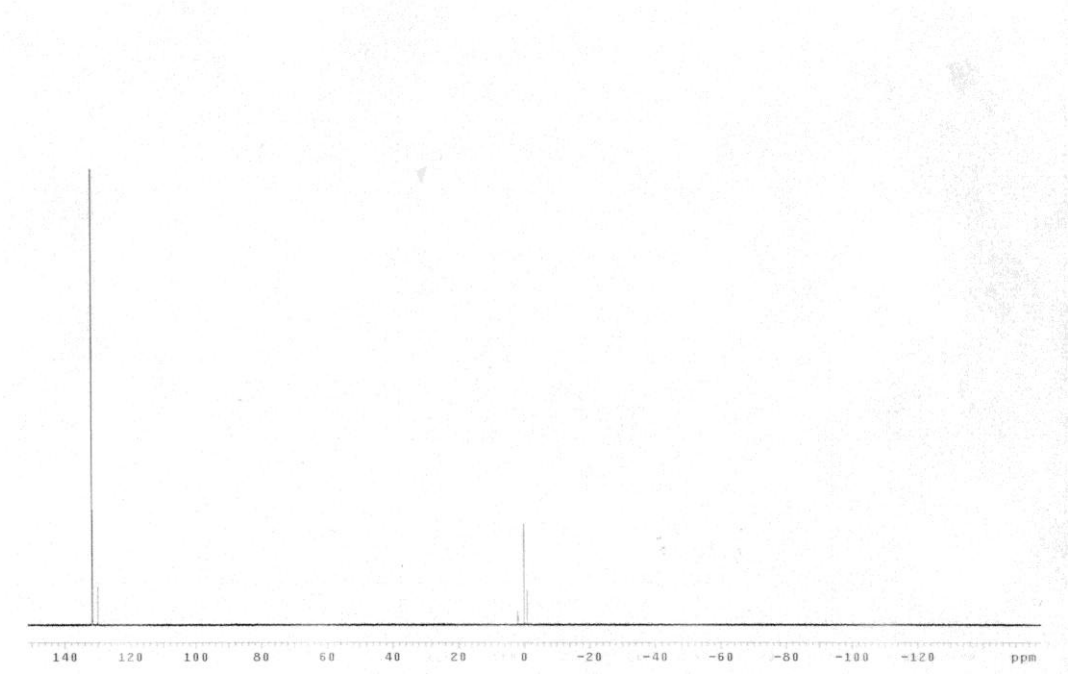
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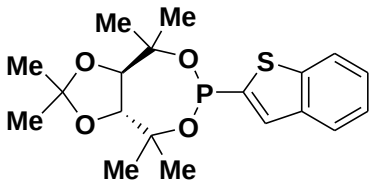

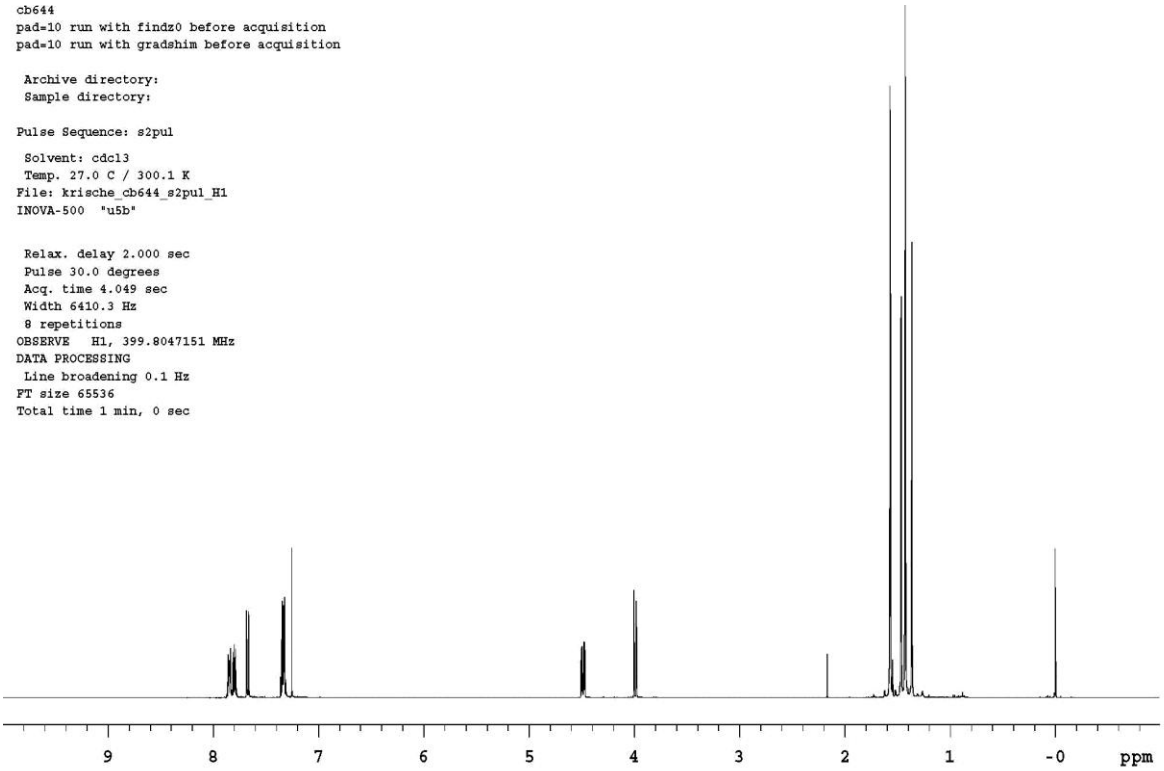

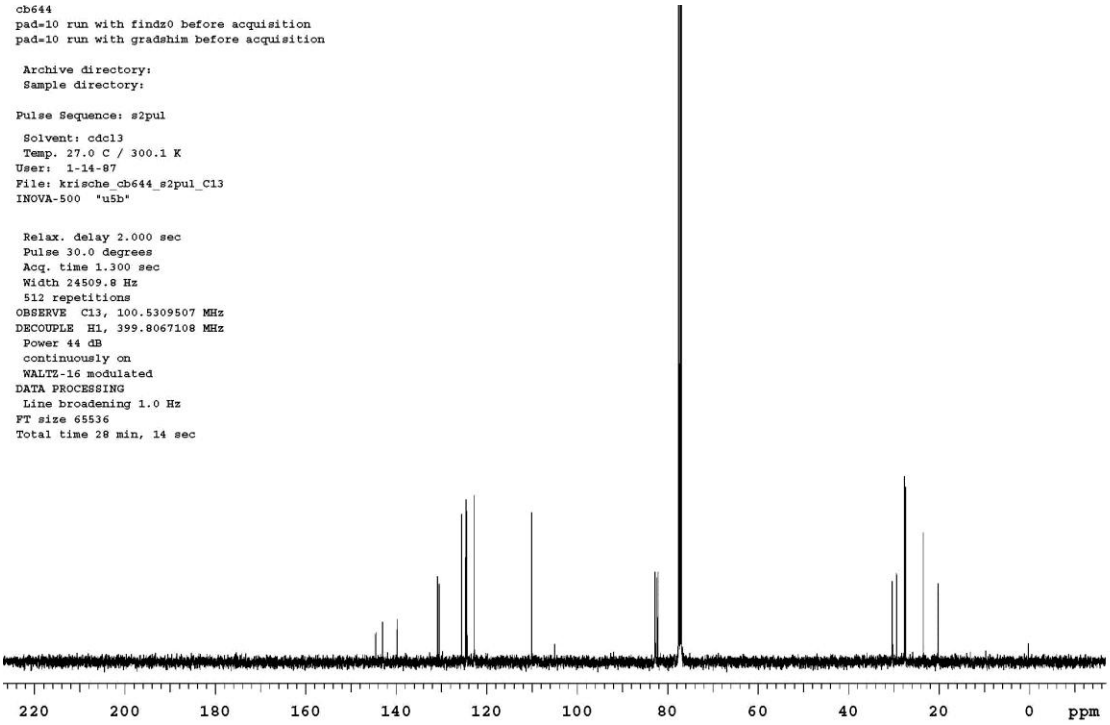
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Line broadening 1.0 Hz
FT size 65536
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80
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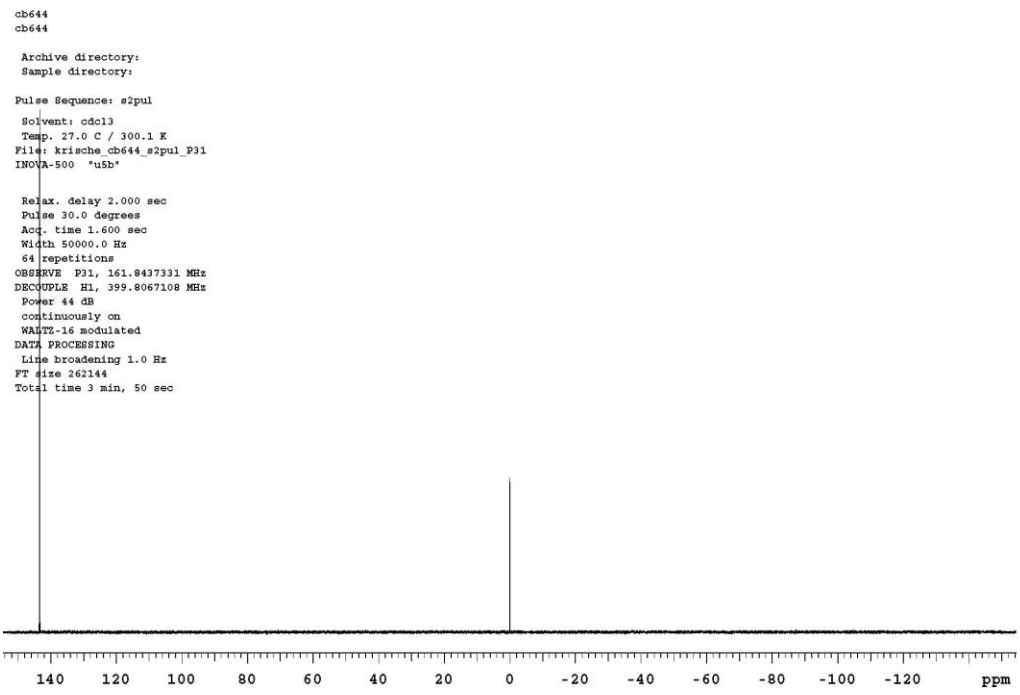
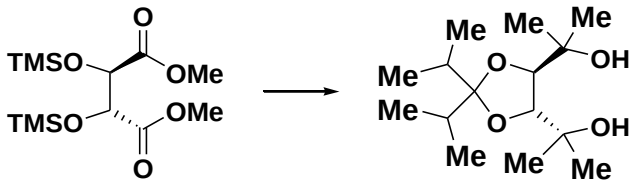
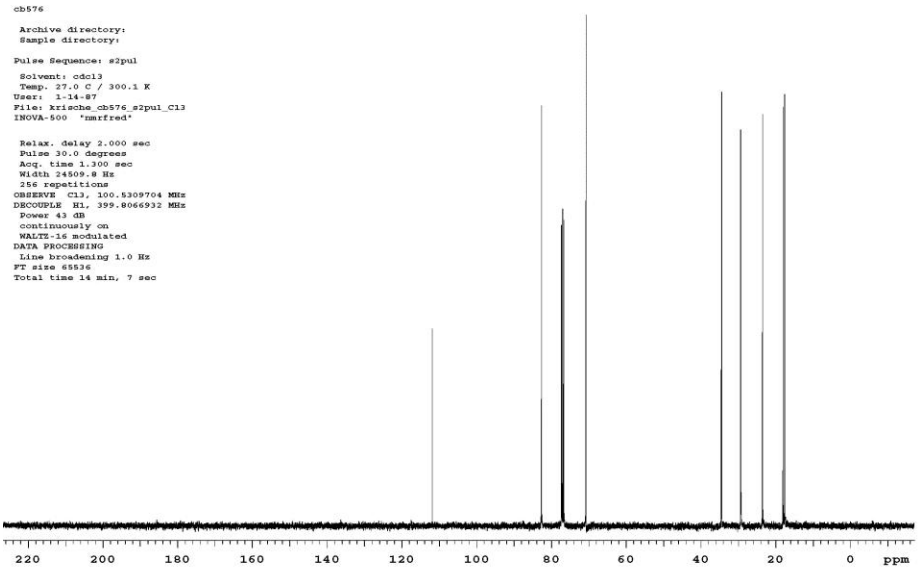
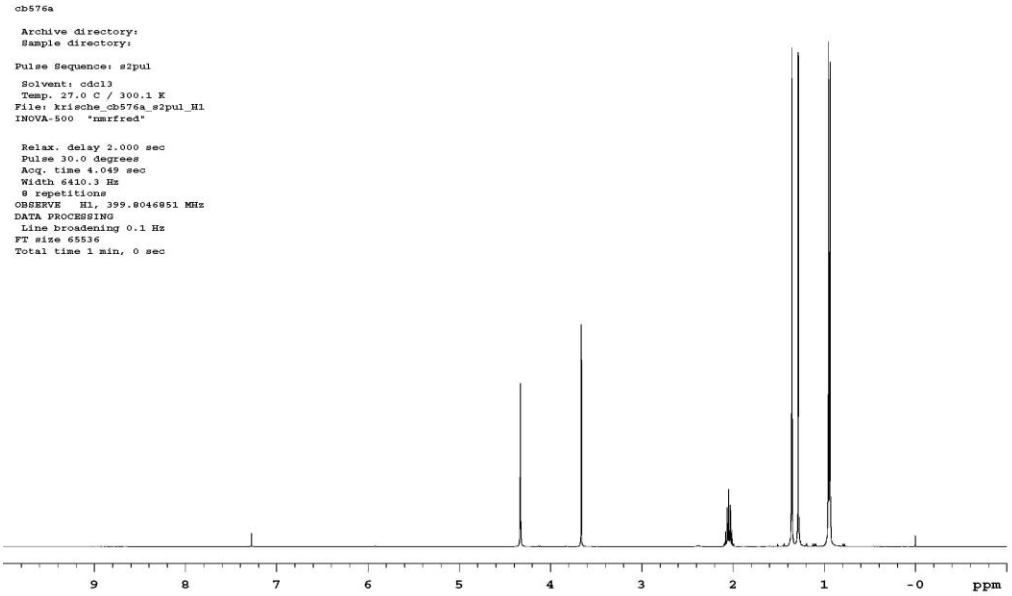
0
ppm


cb644
cb644
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 27.0 C / 300.1 K
File: krische_cb644_s2pul_P31
INOVA-500 "u5b"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.600 sec
Width 50000.0 Hz
64 repetitions
OBSERVE P31, 161.8437331 MHz
DECOUPLE H1, 399.8067108 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 262144
Total time 3 min, 50 sec
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
ppm

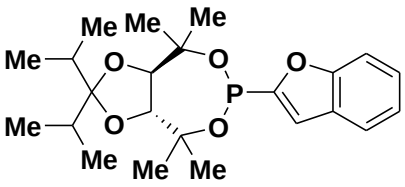
(4*R*,5*R*)-diisopropyl- 2,2-dimethyl-1,3-dioxolane-4,5-dipropan-2-ol

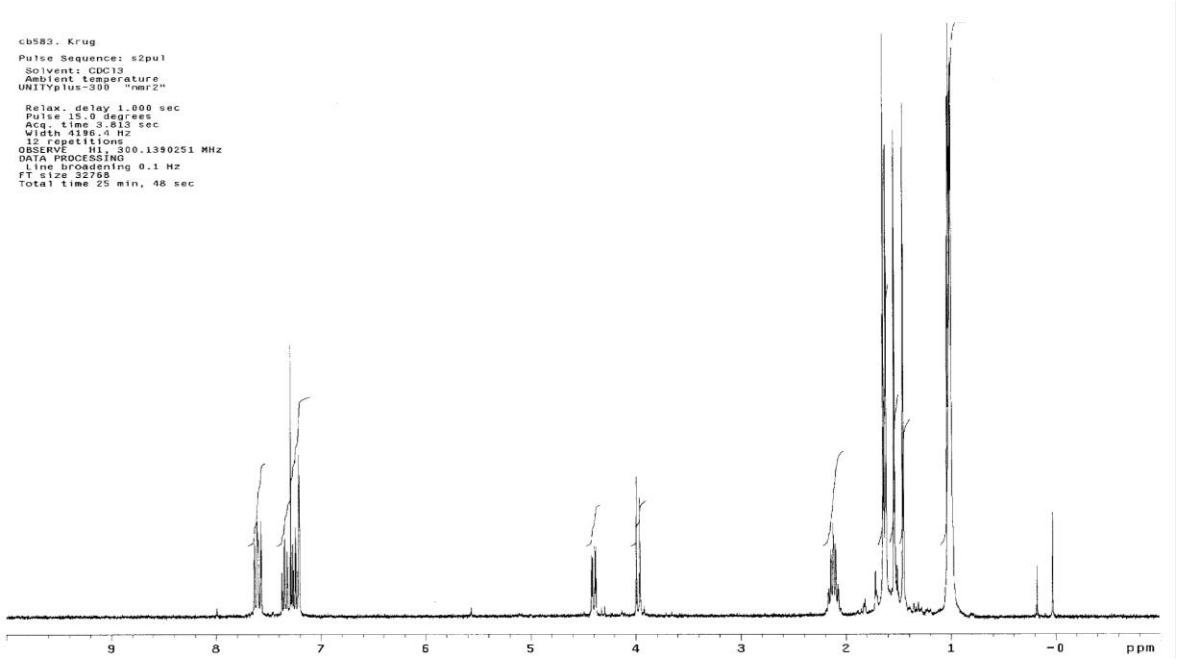


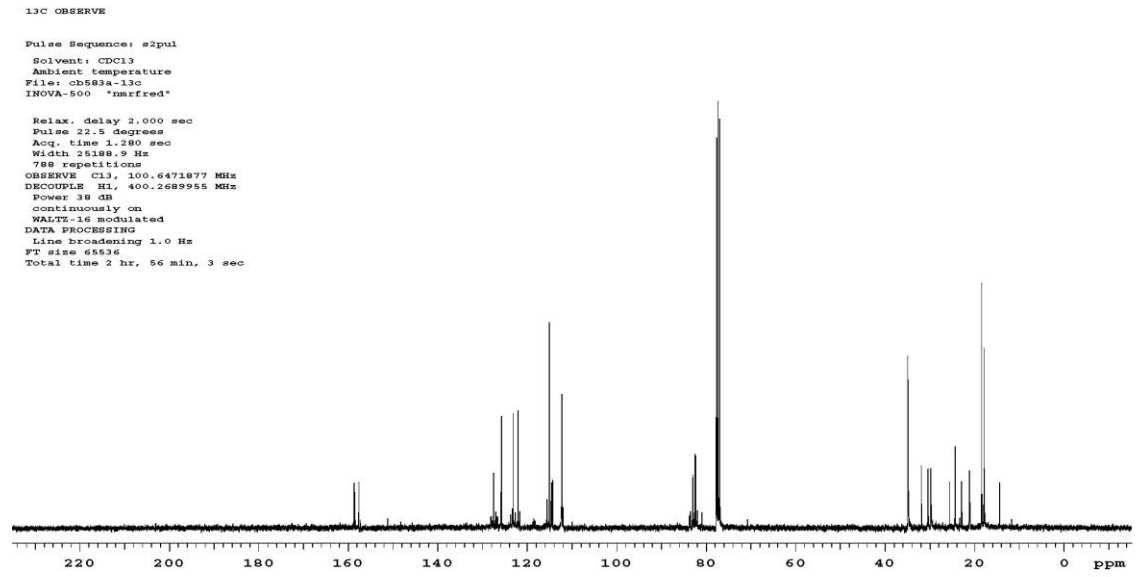


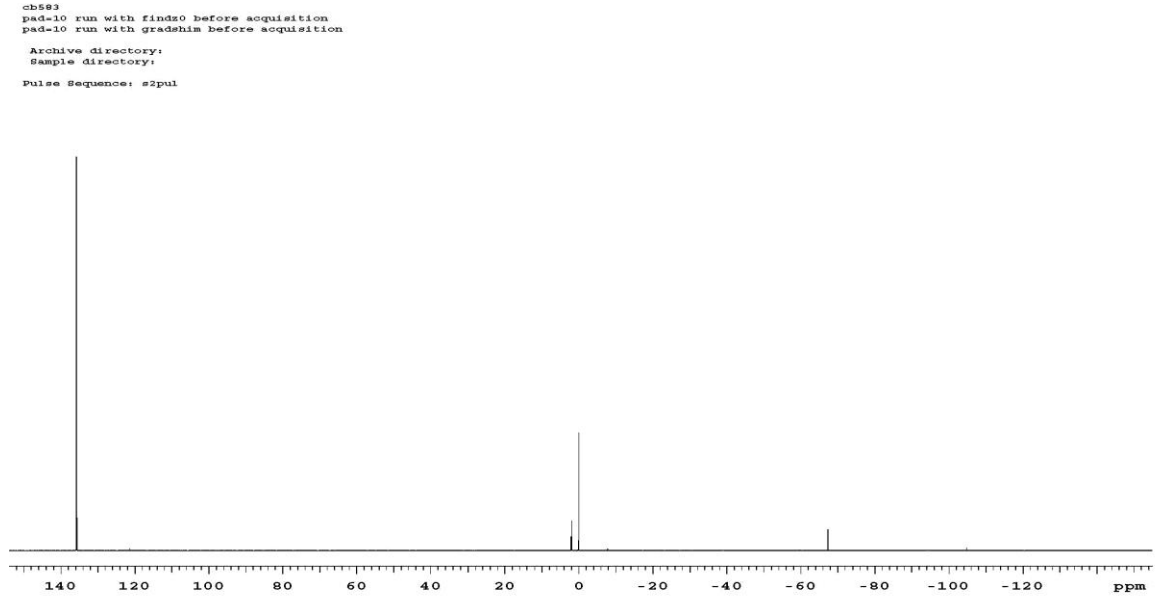


(3a*R*,8a*R*)-6-(benzofuran-2-yl)-tetrahydro-2,2-diisopropyl-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.65

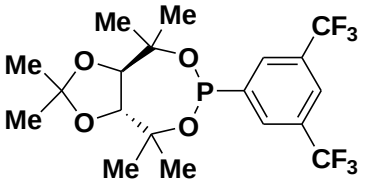


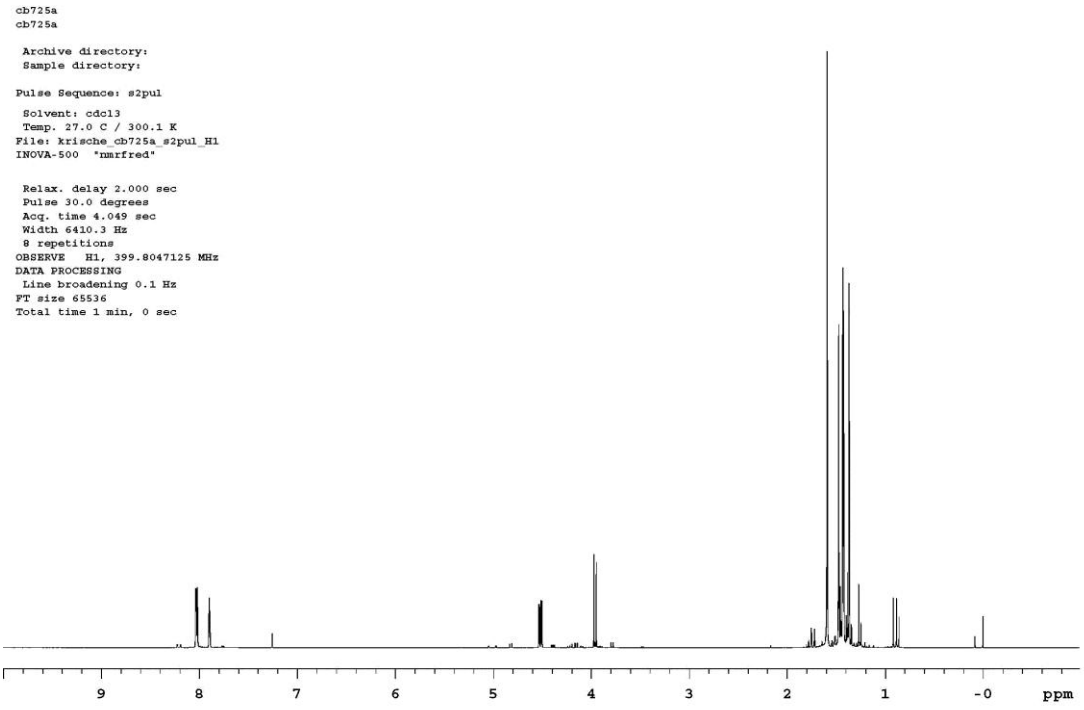


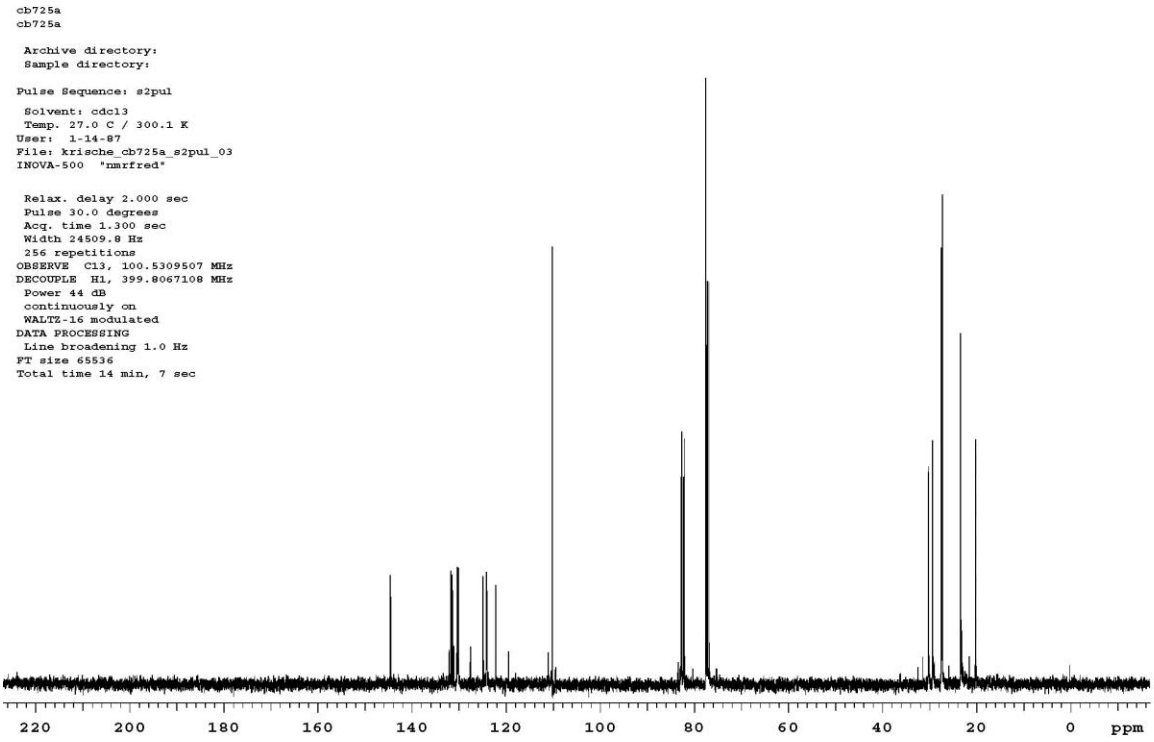

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: cb583a-13c
INOVA-500 "nmrfred"
Relax. delay 2.000 sec
Pulse 22.5 degrees
Acq. time 1.280 sec
Width 25188.9 Hz
788 repetitions
OBSERVE C13, 100.6471877 MHz
DECOUPLE H1, 400.2689955 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 2 hr, 56 min, 3 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

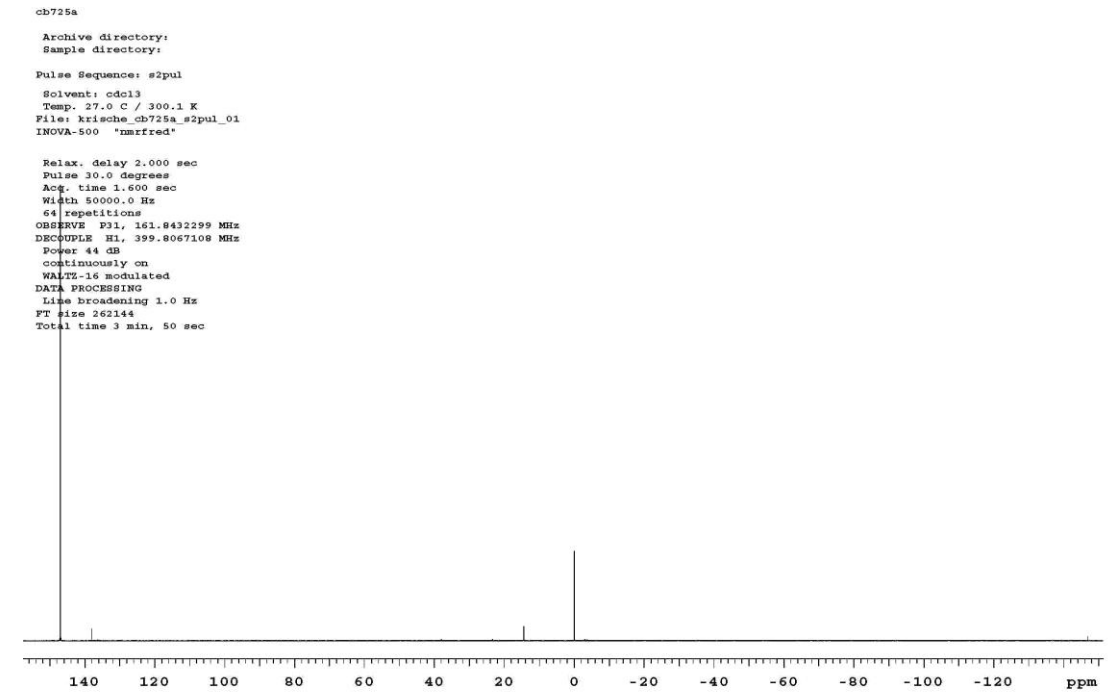

cb583
pad=10 run with findz0 before acquisition
pad=10 run with gradshim before acquisition
Archive directory:
Sample directory:
Pulse Sequence: s2pul
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
ppm

(3a*R*,8a*R*)-6-(3,5-bis(trifluoromethyl)phenyl)-tetrahydro-2,2,4,4,8,8-hexamethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.61

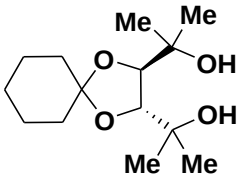


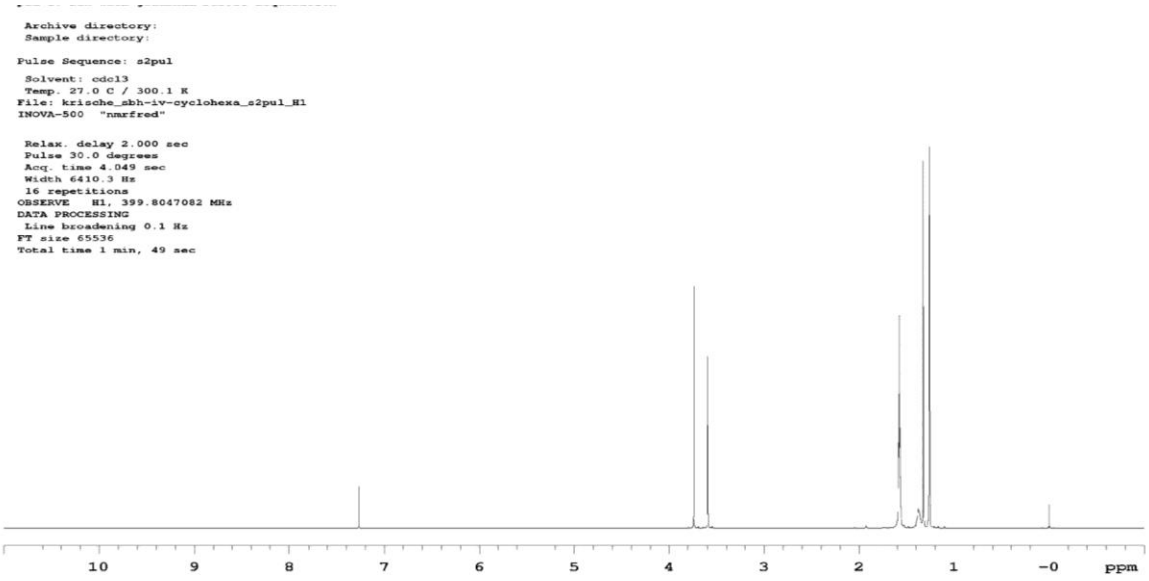


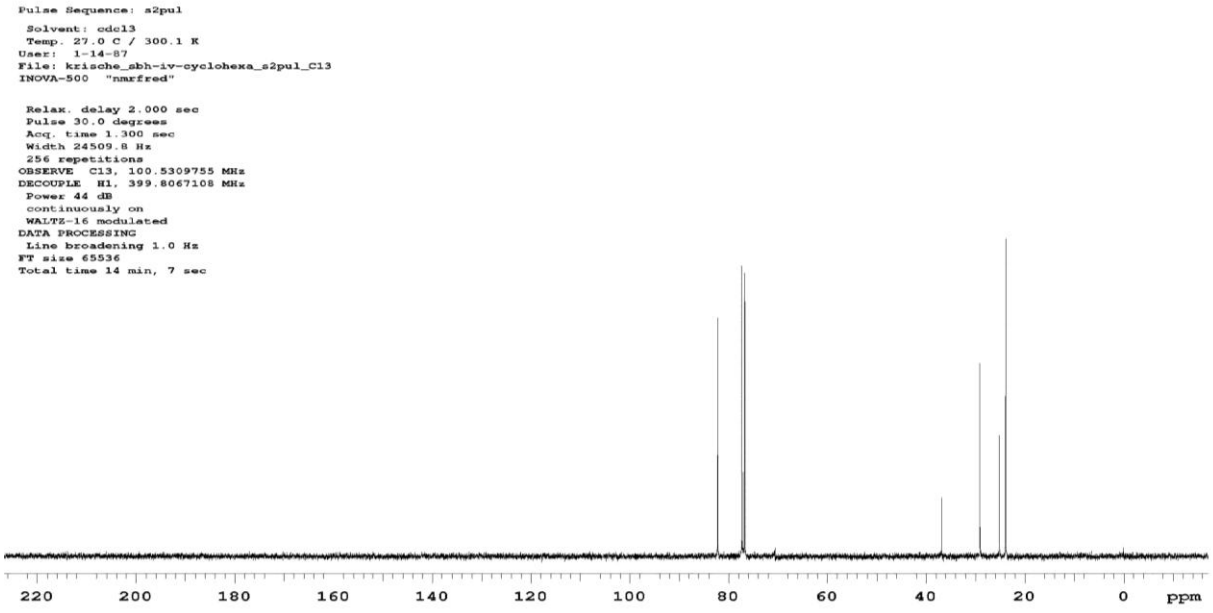

cb725a
cb725a
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 27.0 C / 300.1 K
User: 1-14-87
File: krische_cb725a_s2pul_03
INOVA-500 "nmrfred"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
256 repetitions
OBSERVE C13, 100.5309507 MHz
DECOUPLE H1, 399.8067108 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 14 min, 7 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm


cb725a
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 27.0 C / 300.1 K
File: krische_cb725a_s2pul_01
INOVA-500 "nmrfred"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.600 sec
Width 50000.0 Hz
64 repetitions
OBSERVE P31, 161.8432299 MHz
DECOUPLE H1, 399.8067108 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 262144
Total time 3 min, 50 sec
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
ppm

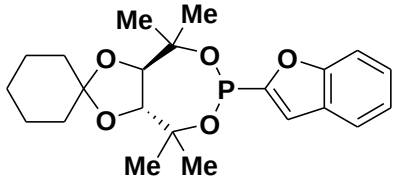
2-[3-(1-Hydroxy-1-methyl-ethyl)-1,4-dioxa-spiro[4.5]dec-2-yl]-propan-2-ol

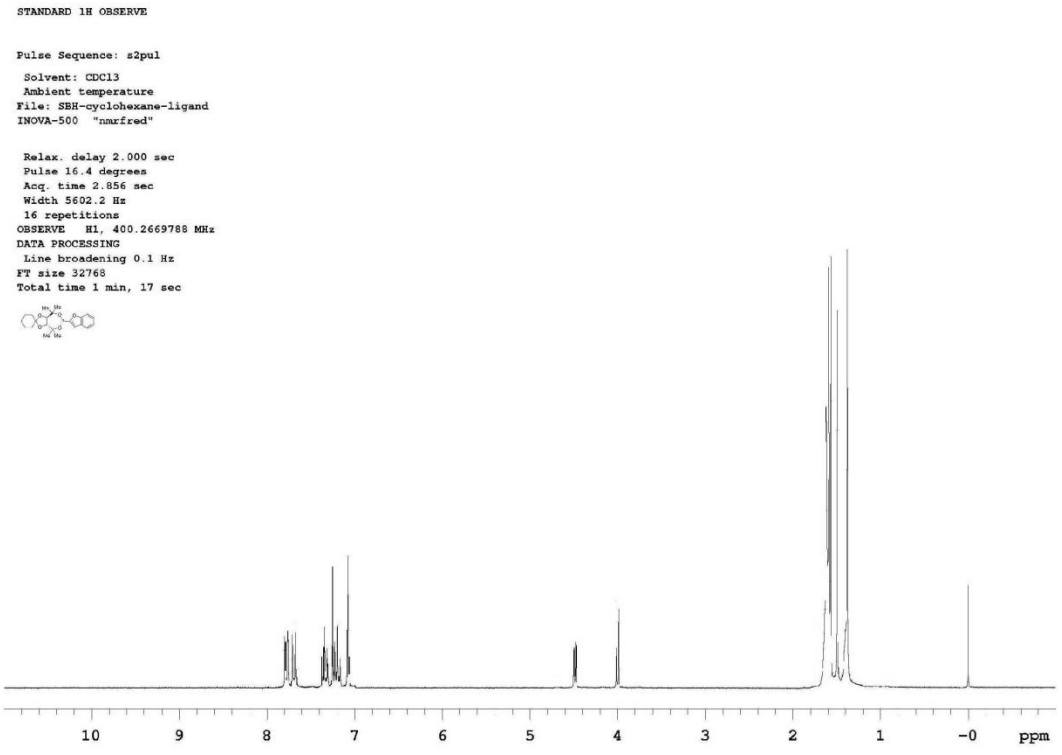


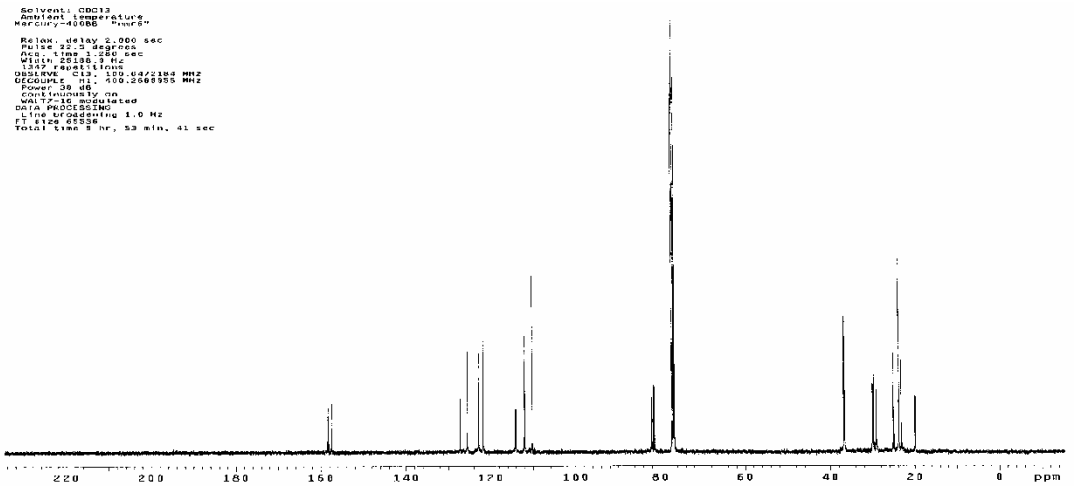


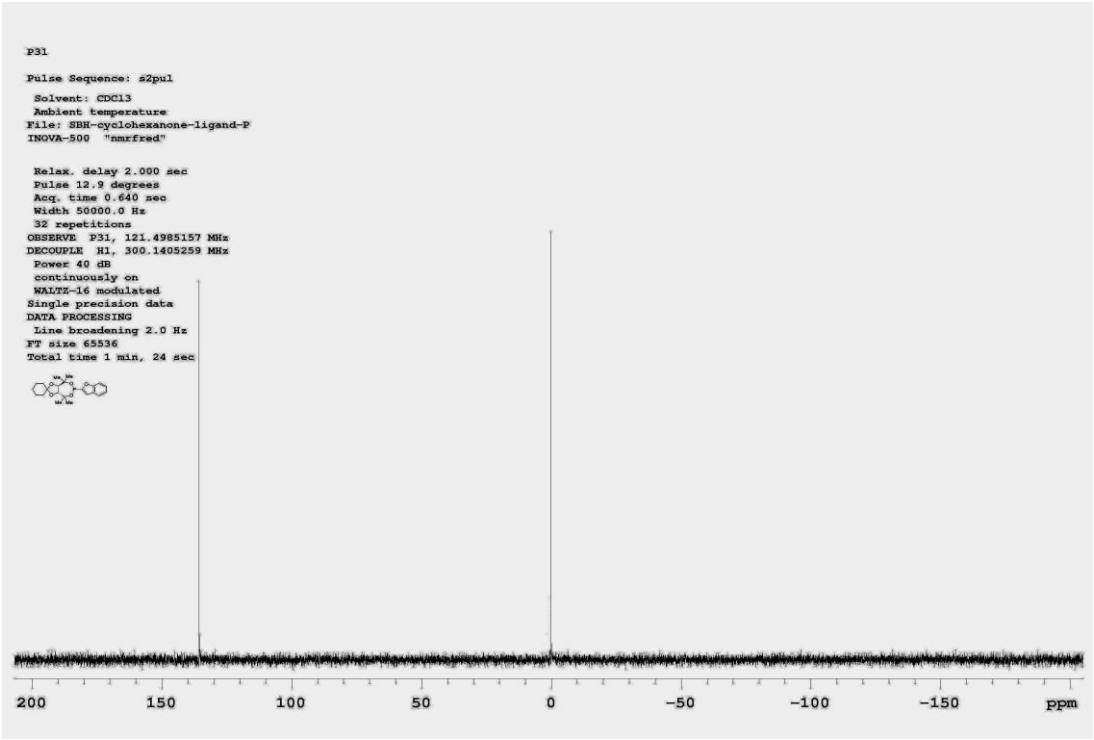


(3a*R*,8a*R*)-6-(benzofuran-2-yl)-2,2-cyclohexyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.66

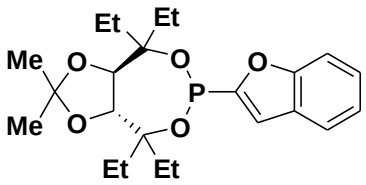


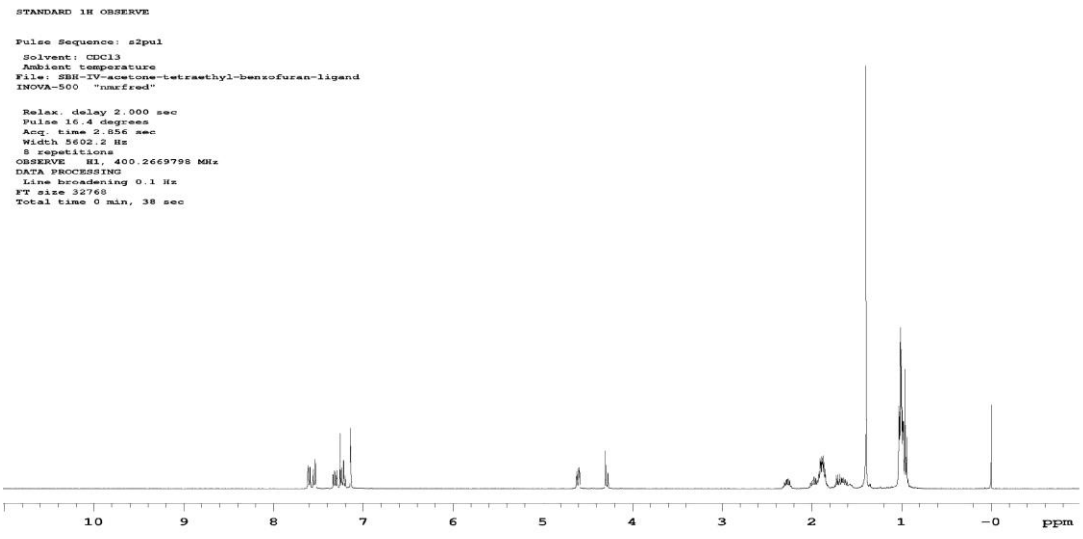


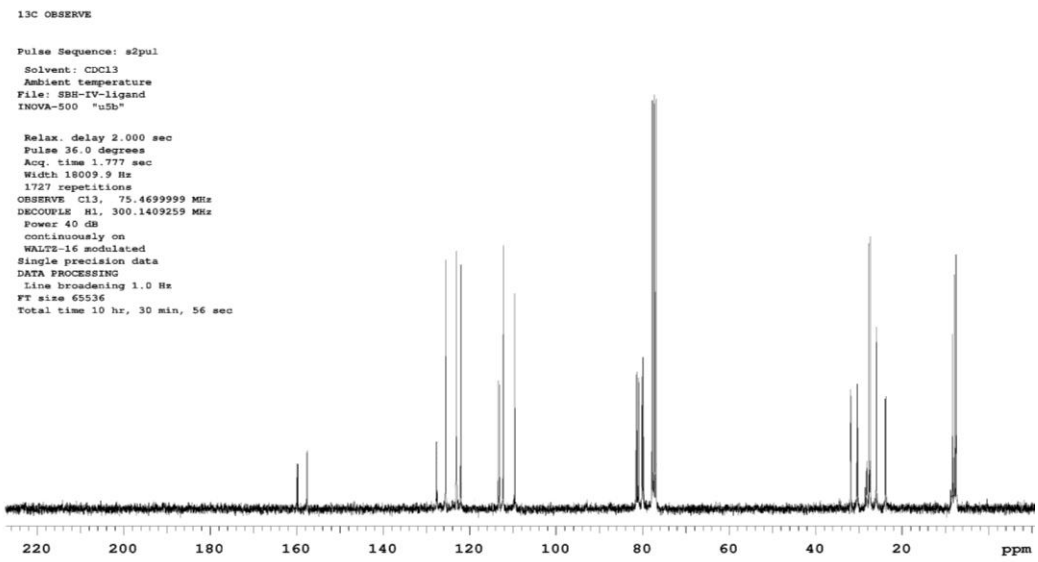

Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"
Relax. delay 2.000 sec
Pulse 22.5 degrees
Acq. time 1.280 sec
Width 20188.9 Hz
1347 repetitions
OBSERVE C13, 100.6472184 MHz
DECOUPL5 H1, 400.2668955 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 5 hr, 53 min, 41 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

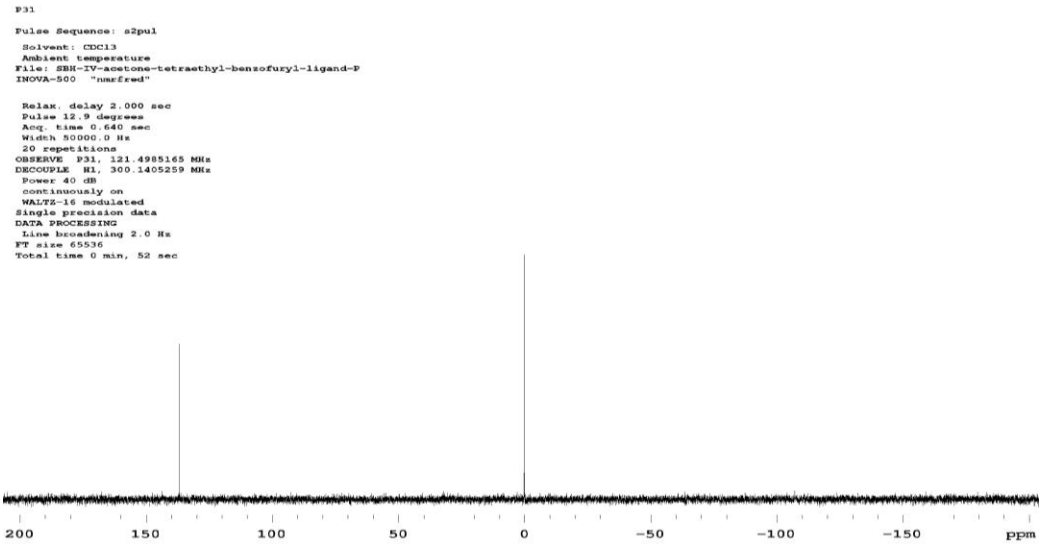

P31
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: SBH-cyclohexanone-ligand-P
INOVA-500 "nmrfred"
Relax. delay 2.000 sec
Pulse 12.9 degrees
Acq. time 0.640 sec
Width 50000.0 Hz
32 repetitions
OBSERVE P31, 121.4985157 MHz
DECOUPLE H1, 300.1405259 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
Single precision data
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 1 min, 24 sec
200
150
100
50
0
-50
-100
-150
ppm

(3a*R*,8a*R*)-6-(benzofuran-2-yl)-4,4,8,8-tetraethyl-tetrahydro-2,2-dimethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.62

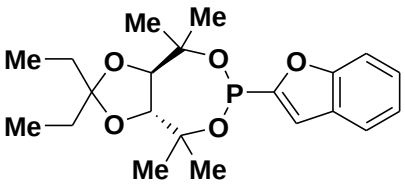


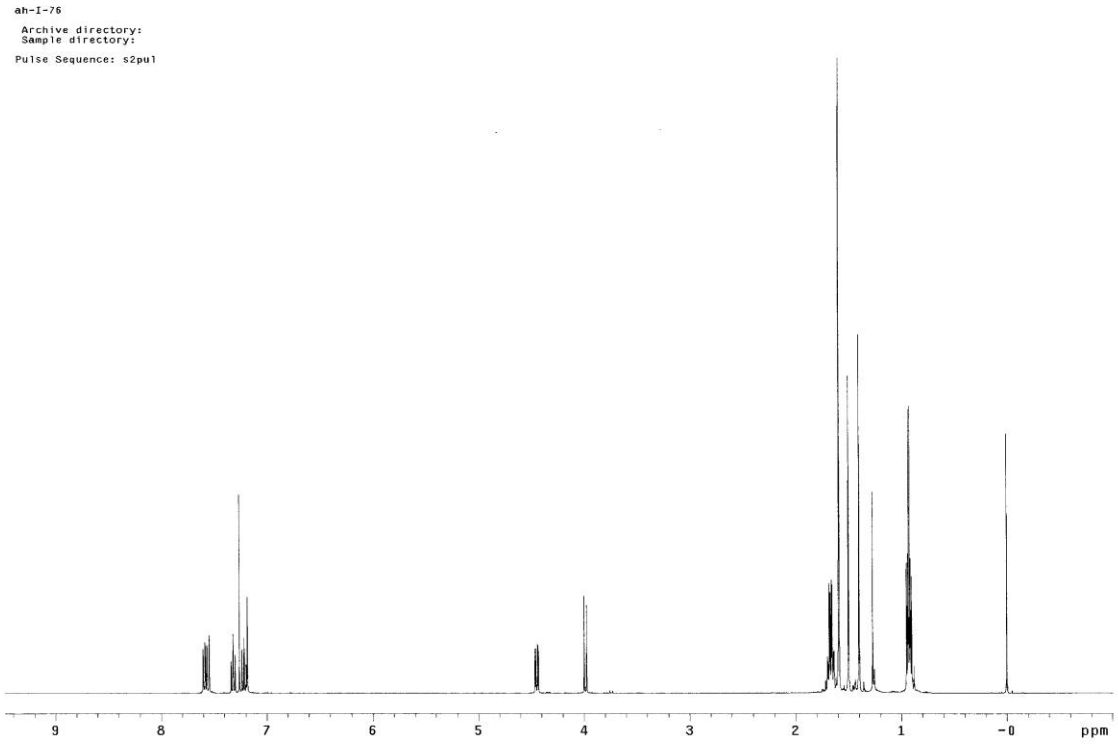


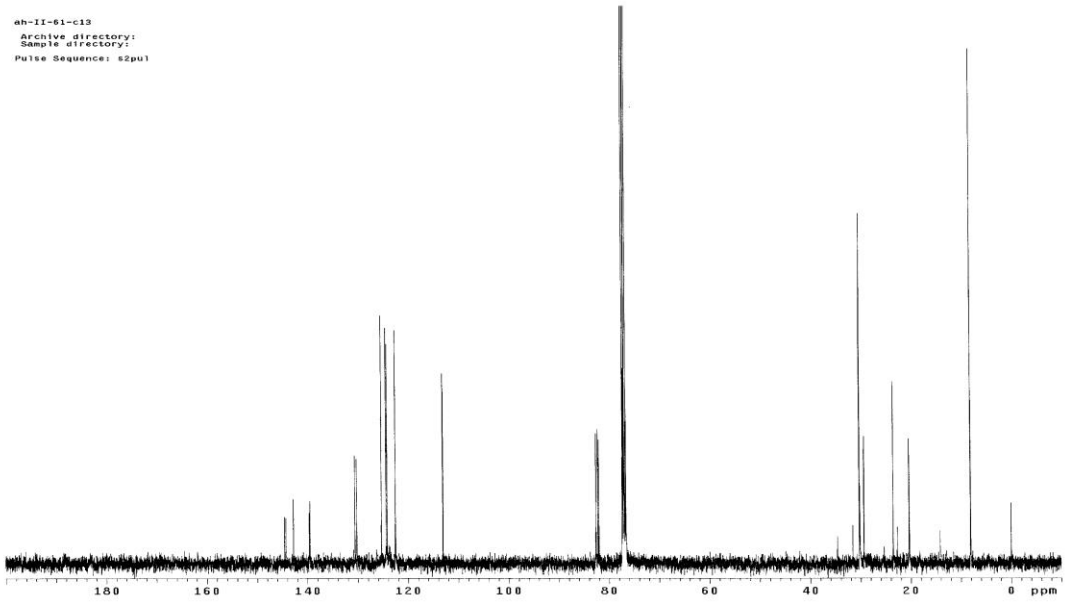

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: SBH-IV-ligand
INOVA-500 "u5b"
Relax. delay 2.000 sec
Pulse 36.0 degrees
Acq. time 1.777 sec
Width 18009.9 Hz
1727 repetitions
OBSERVE C13, 75.4699999 MHz
DECOUPLE H1, 300.1409259 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
Single precision data
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 10 hr, 30 min, 56 sec
220
200
180
160
140
120
100
80
60
40
20
ppm

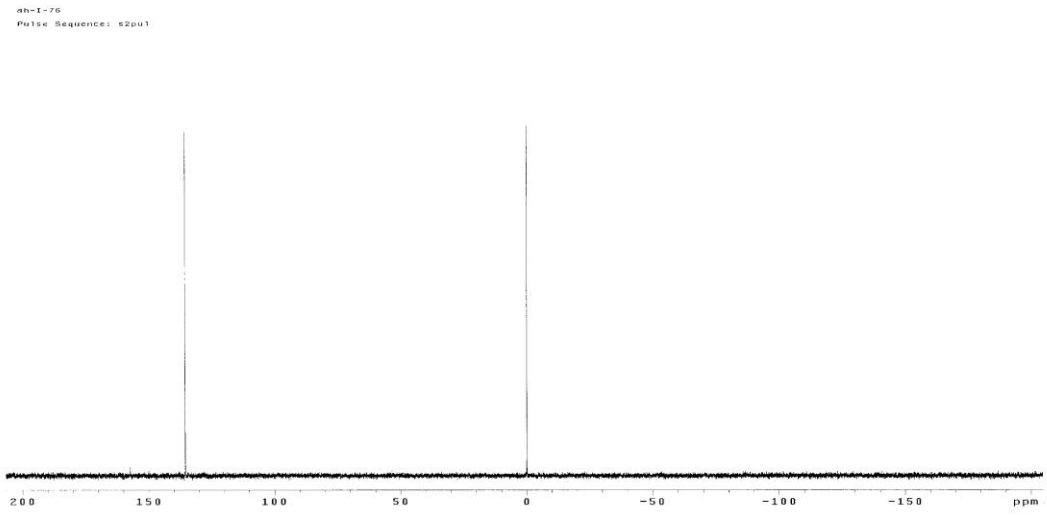

P31
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: SBH-IV-acetone-tetraethyl-benzofuryl-ligand-P
INOVA-500 "nmrfred"
Relax. delay 2.000 sec
Pulse 12.9 degrees
Acq. time 0.640 sec
Width 50000.0 Hz
20 repetitions
OBSERVE P31, 121.4985165 MHz
DECOUPLE H1, 300.1405259 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
Single precision data
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 0 min, 52 sec
200
150
100
50
0
-50
-100
-150
ppm

(3a*R*,8a*R*)-6-(benzofuran-2-yl)-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, 2.64

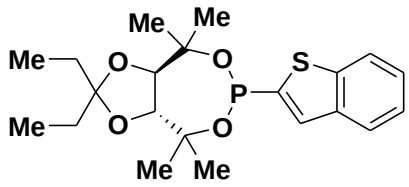


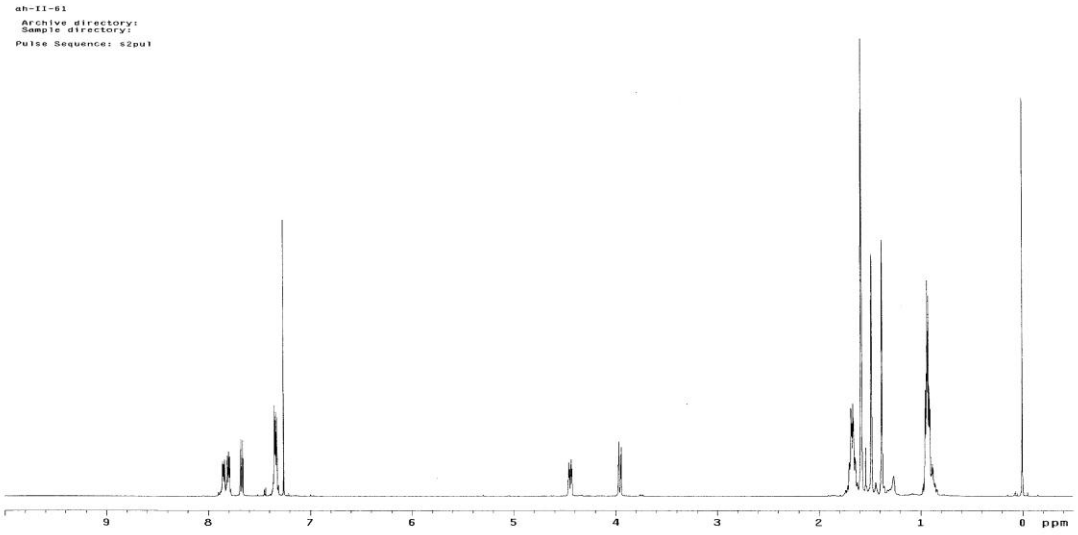


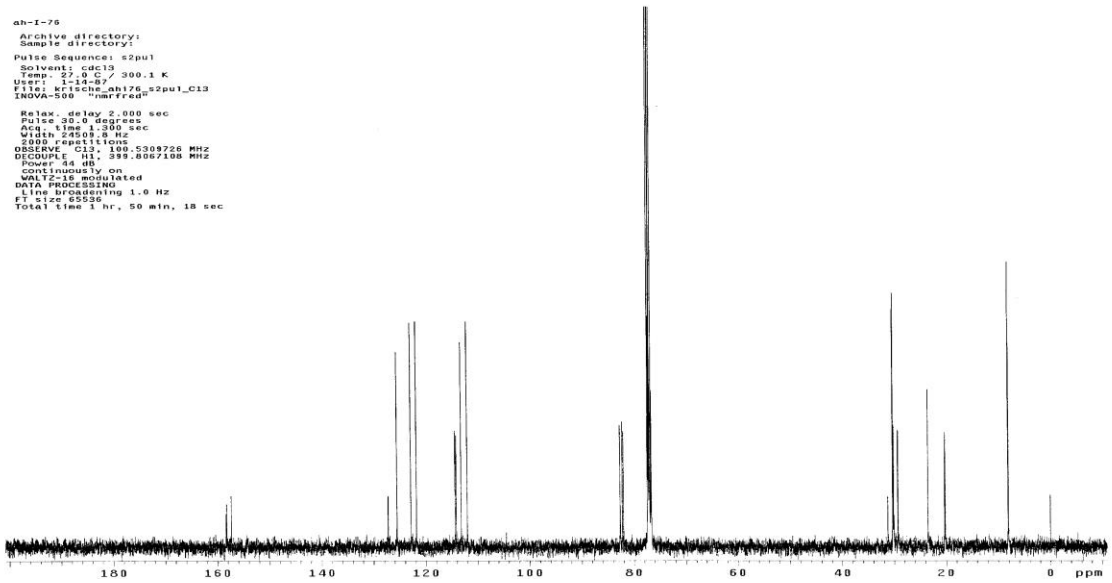

ah-II-61-c13
Archive directory:
Sample directory:
Pulse Sequence: s2pul
180
160
140
120
100
80
60
40
20
0
ppm

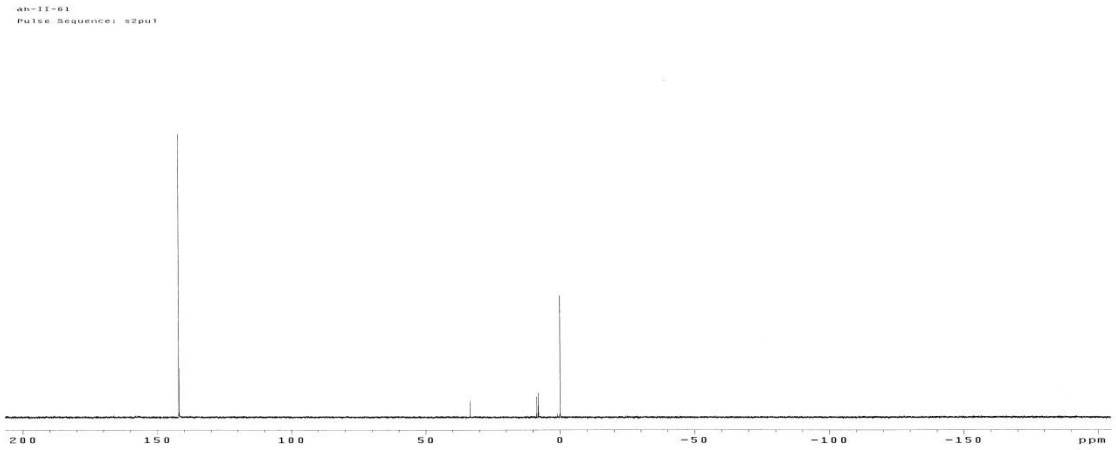

ah-I-76
Pulse Sequence: s2pul
200
150
100
50
0
-50
-100
-150
ppm

(3a*R*,8a*R*)-6-(benzo[b]thiophen-2-yl)-2,2-diethyl-tetrahydro-4,4,8,8-tetramethyl-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, AP-I

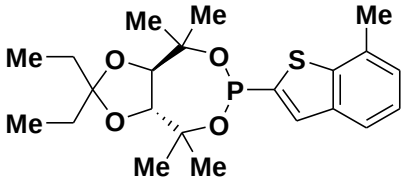


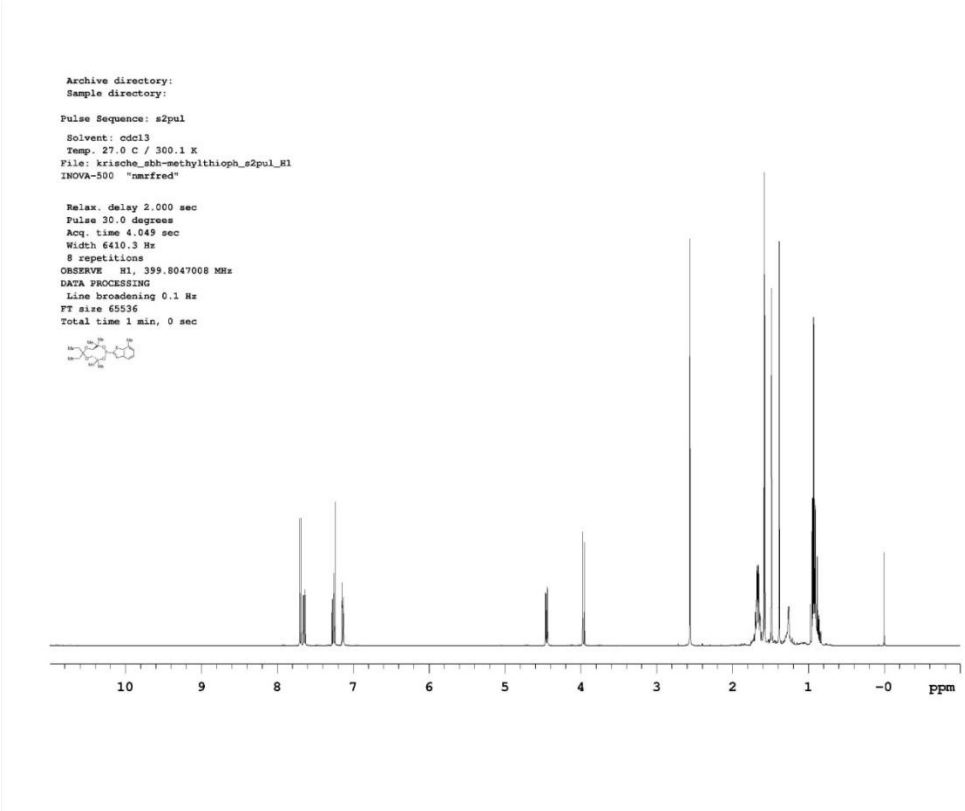


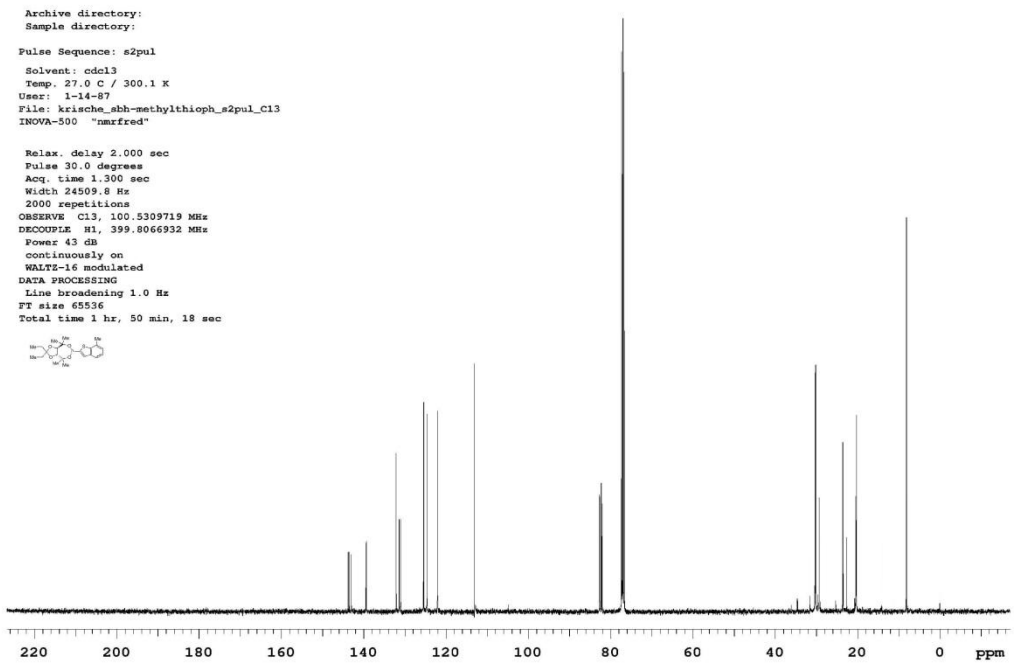

ah-I-76
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 27.0 C / 300.1 K
User: 1-14-87
File: krische_ah176_s2pul_C13
INOVA-500 "marfred"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
2000 repetitions
OBSERVE C13, 100.5309726 MHz
DECOUPLE H1, 399.8067108 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 1 hr, 50 min, 18 sec
180
160
140
120
100
80
60
40
20
0
ppm

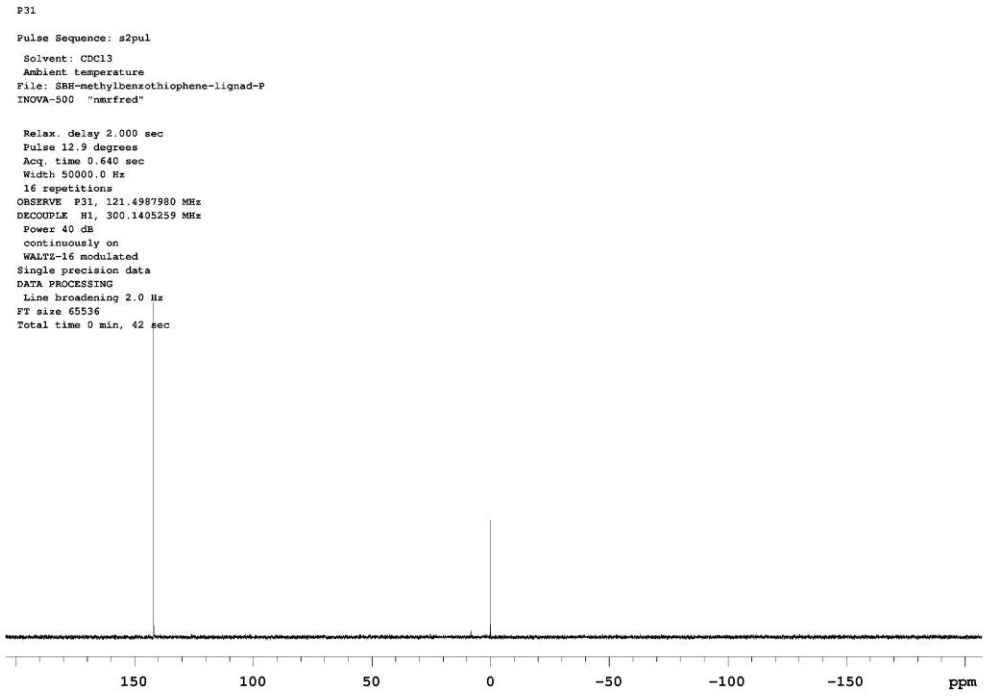

ah-II-61
Pulse Sequence: s2pul
200
150
100
50
0
-50
-100
-150
ppm

(3a*R*,8a*R*)-2,2-diethyl-4,4,8,8-tetramethyl-6-(7-methylbenzo[b]thiophen-2-yl)-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, AP-II

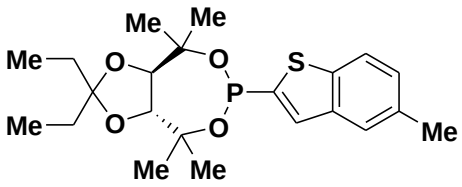


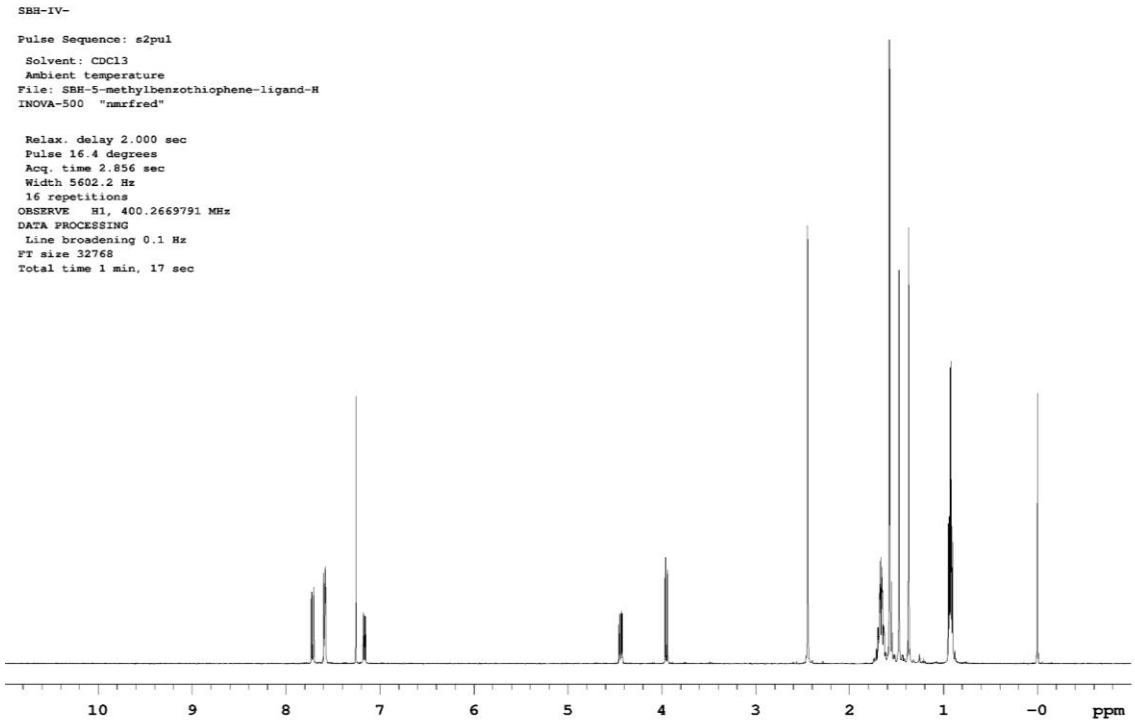


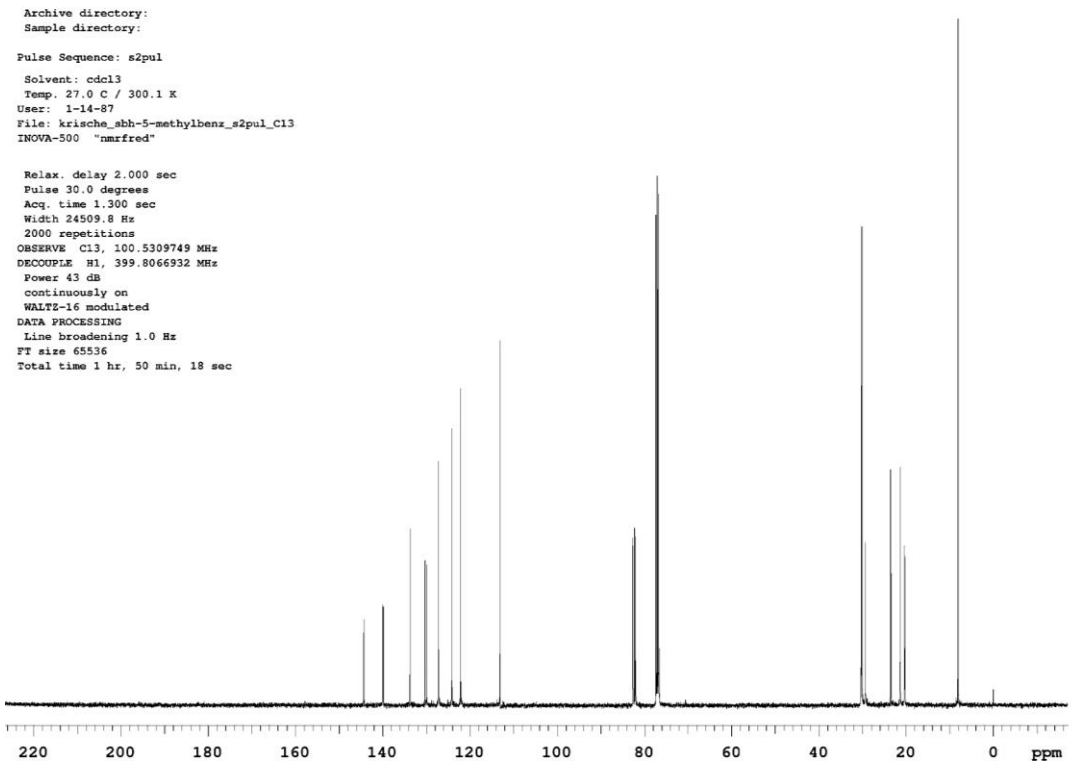

Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 27.0 C / 300.1 K
User: 1-14-87
File: krische_sbh-methylthioph_s2pul_C13
INOVA-500 "nmrfred"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
2000 repetitions
OBSERVE C13, 100.5309719 MHz
DECOUPLE H1, 399.8066932 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 1 hr, 50 min, 18 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

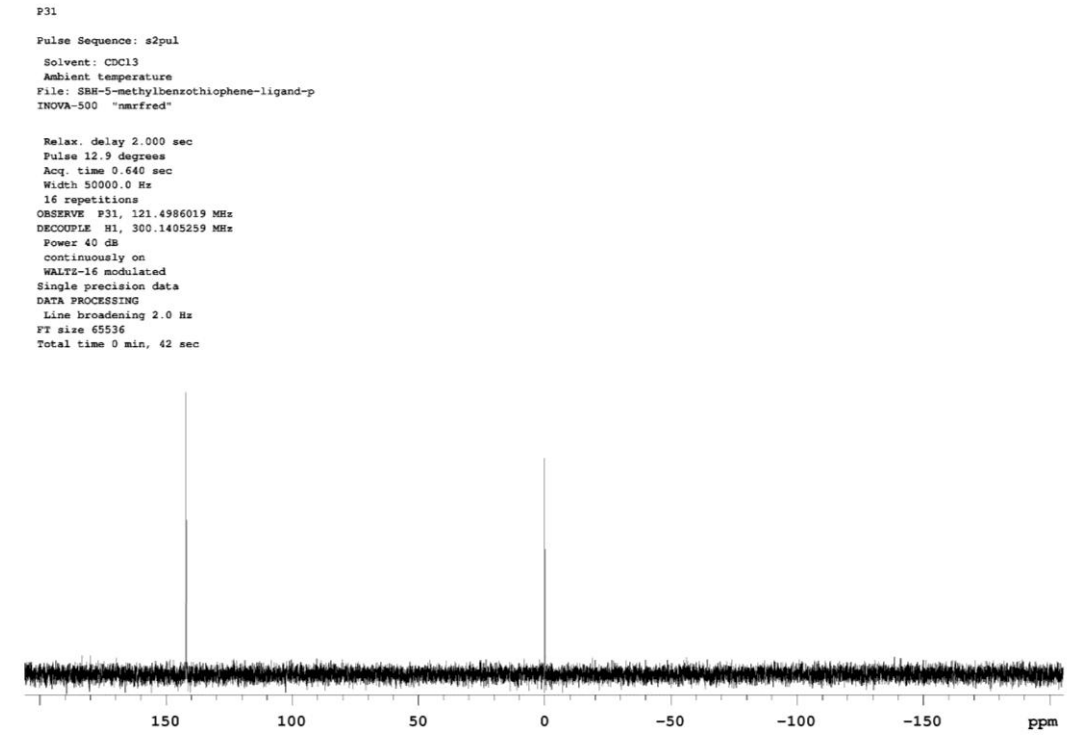

P31
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: SBH-methylbenzothiophene-lignad-P
INOVA-500 "nmrfred"
Relax. delay 2.000 sec
Pulse 12.9 degrees
Acq. time 0.640 sec
Width 50000.0 Hz
16 repetitions
OBSERVE P31, 121.4987980 MHz
DECOUPLE H1, 300.1405259 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
Single precision data
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 0 min, 42 sec
150
100
50
0
-50
-100
-150
ppm

(3a*R*,8a*R*)-2,2-diethyl-4,4,8,8-tetramethyl-6-(5-methylbenzo[b]thiophen-2-yl)-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine, AP-III

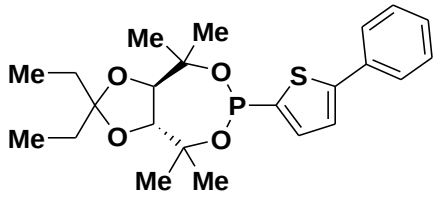


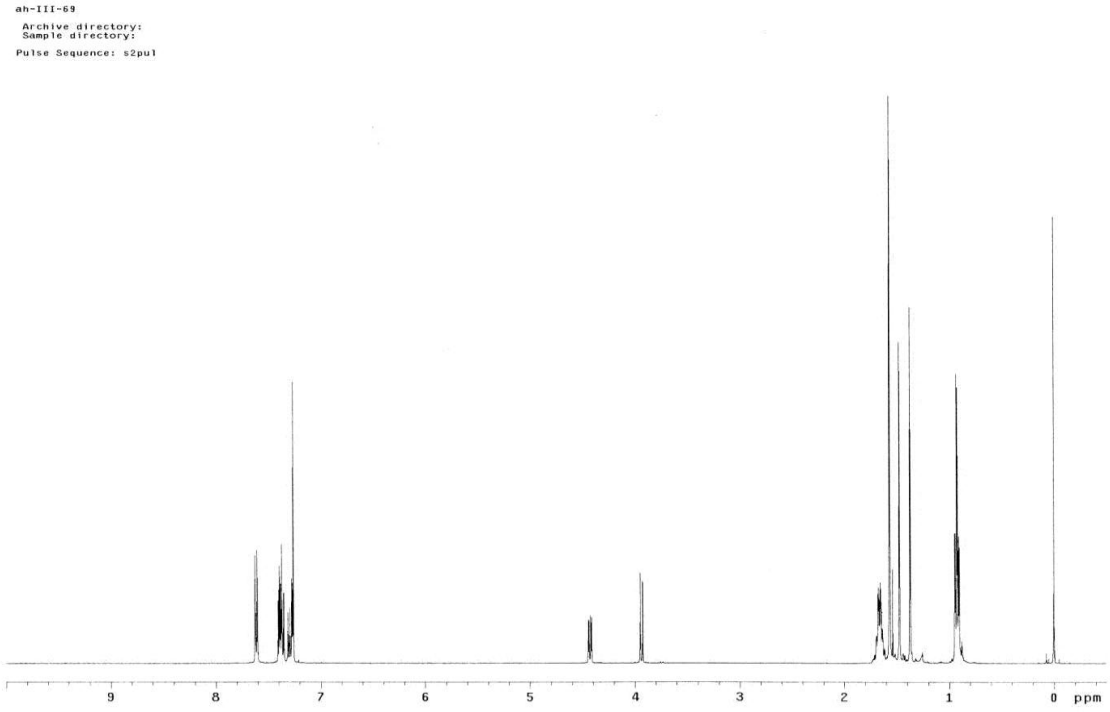


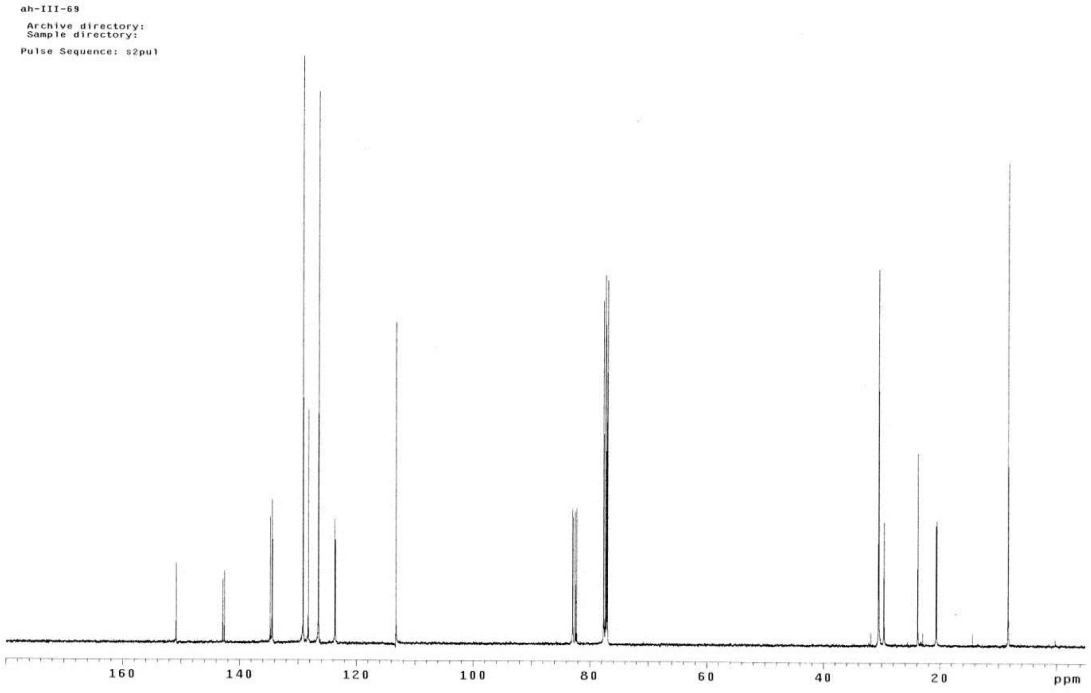

Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 27.0 C / 300.1 K
User: 1-14-87
File: krische_sbh-5-methylbenz_s2pul_C13
INOVA-500 "nmrfred"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
2000 repetitions
OBSERVE C13, 100.5309749 MHz
DECOUPLE H1, 399.8066932 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 1 hr, 50 min, 18 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm


P31
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: SBH-5-methylbenzothiophene-ligand-p
INOVA-500 "nmrfred"
Relax. delay 2.000 sec
Pulse 12.9 degrees
Acq. time 0.640 sec
Width 50000.0 Hz
16 repetitions
OBSERVE P31, 121.4986019 MHz
DECOUPLE H1, 300.1405259 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
Single precision data
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 0 min, 42 sec
150
100
50
0
-50
-100
-150
ppm

(3a*R*,8a*R*)-2,2-diethyl-4,4,8,8-tetramethyl-6-(5-phenylthiophen-2-yl)-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine, AP-IV

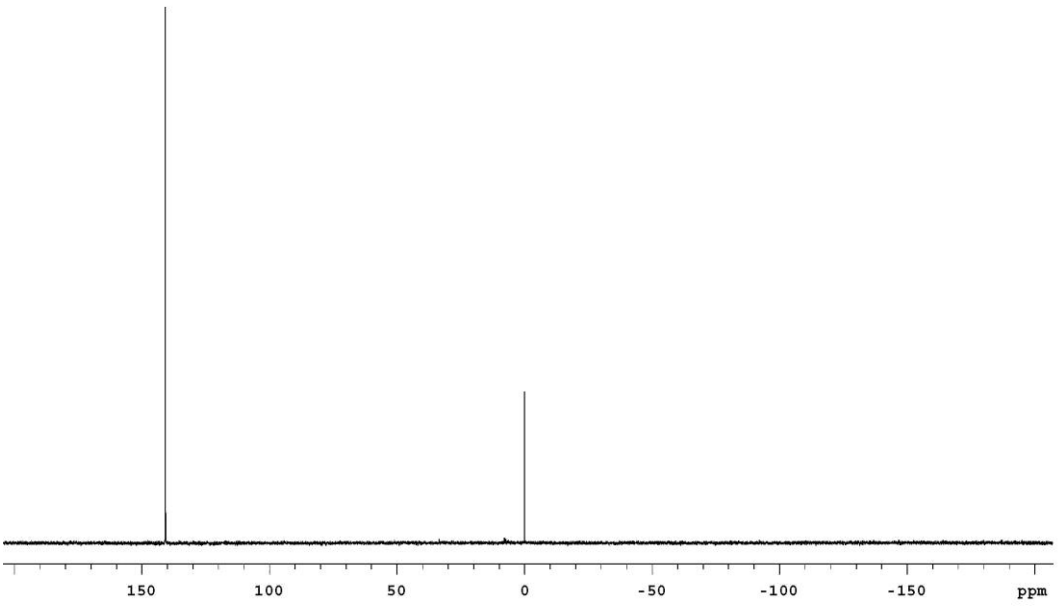






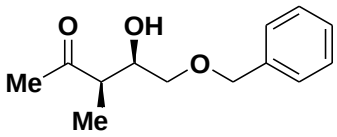
ah-III-69

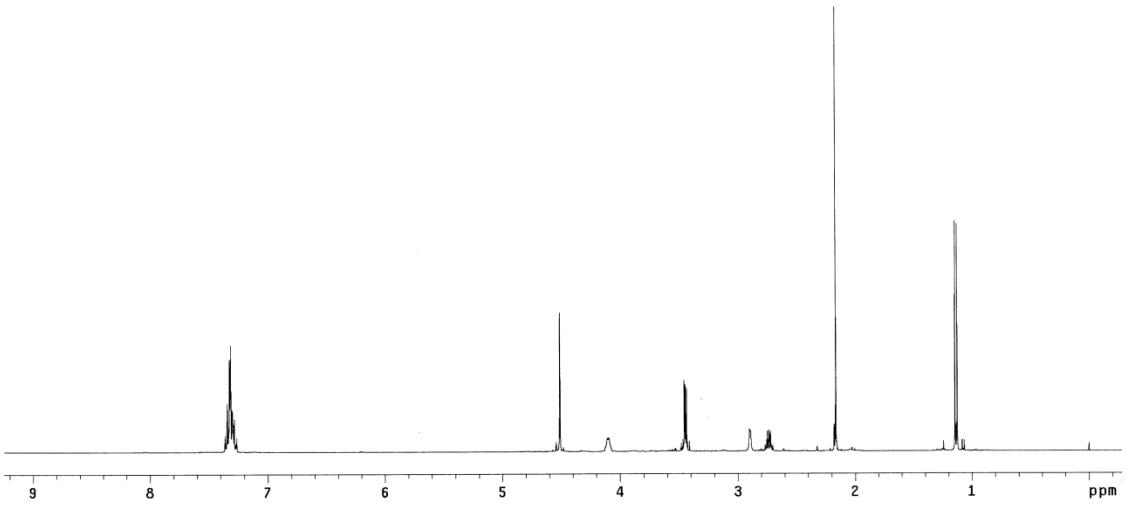
Pulse Sequence: s2pul

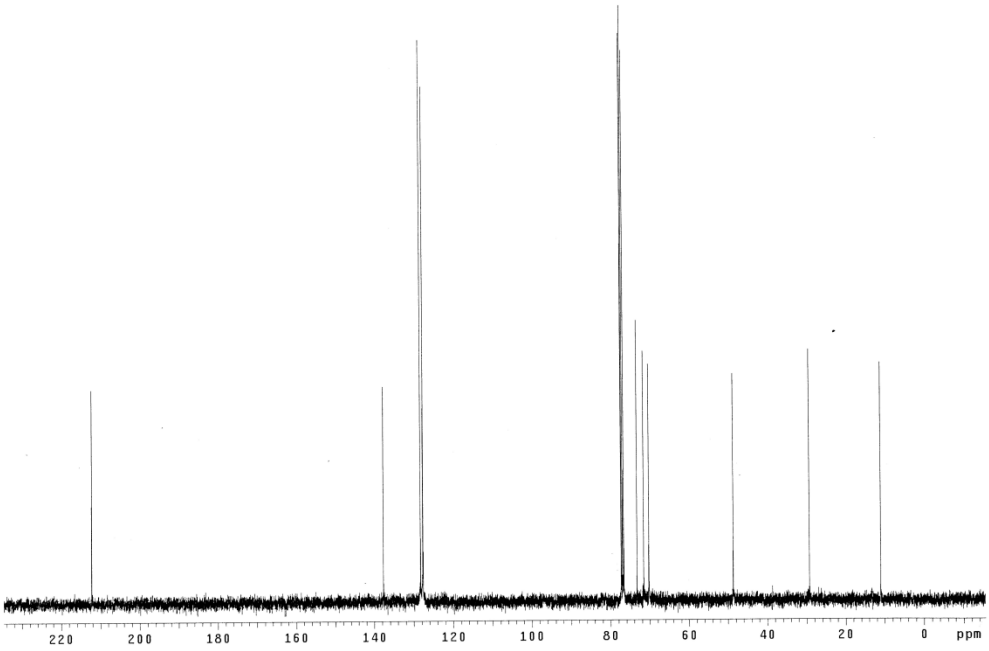


III Spectroscopic Data for the Aldol Products

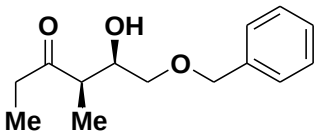
(3*R*,4*R*)-5-(benzyloxy)-4-hydroxy-3-methylpentan-2-one, 2.42

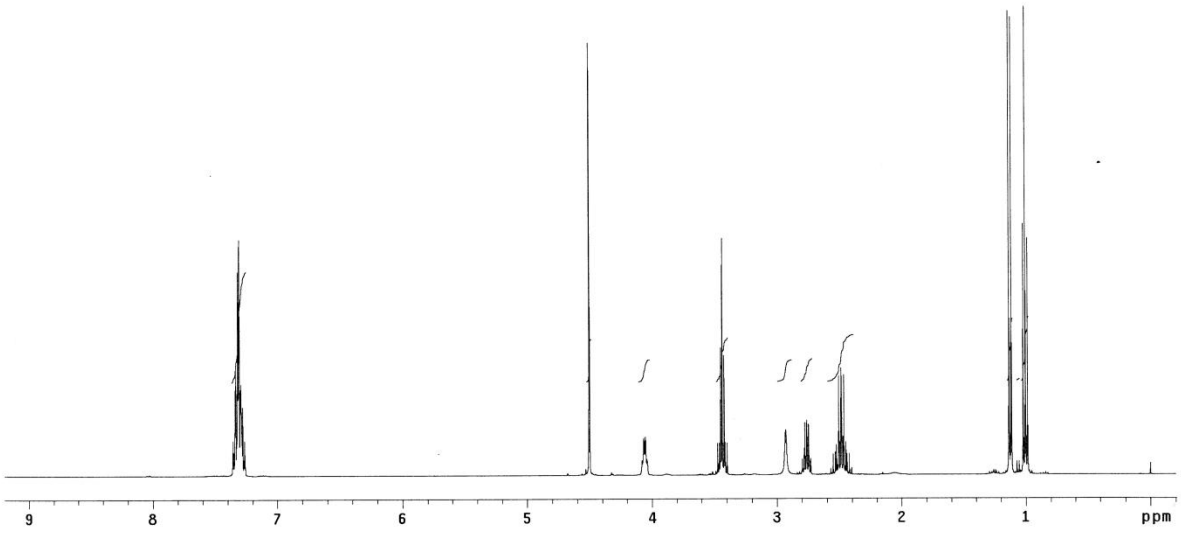


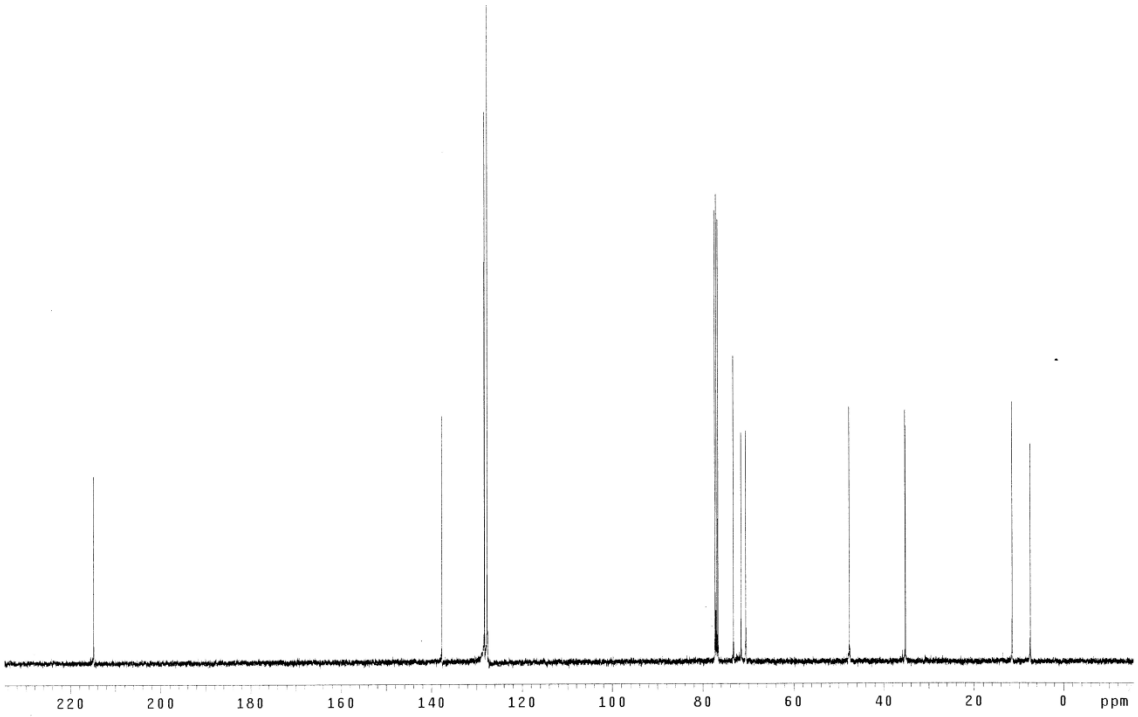




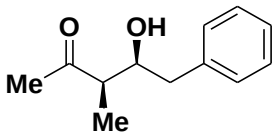
(4*R*,5*R*)-6-(benzyloxy)-5-hydroxy-4-methylhexan-3-one, 2.42a

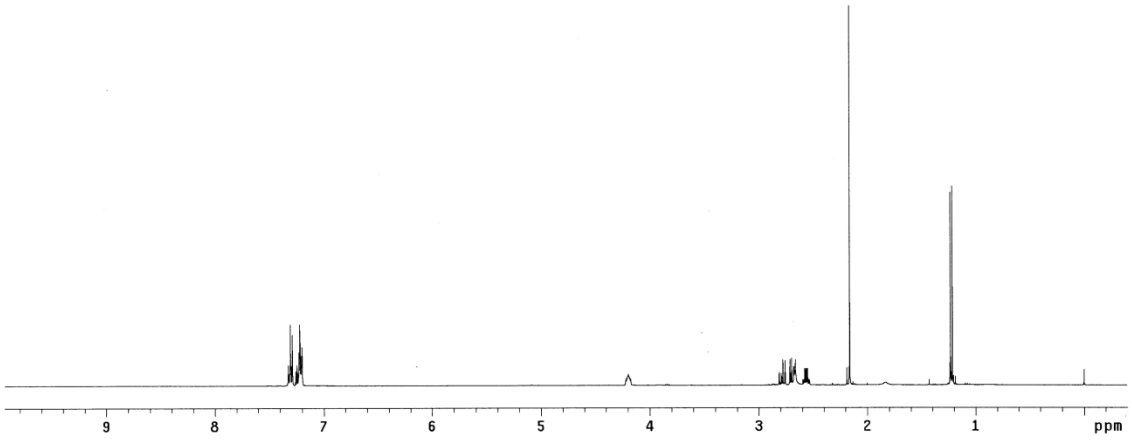


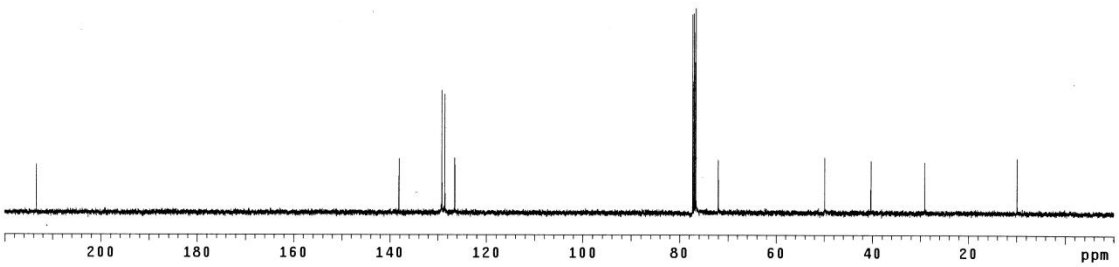




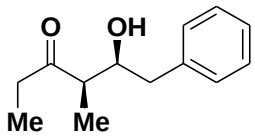
3*R*,4*S*)-4-hydroxy-3-methyl-5-phenylpentan-2-one, 2.70

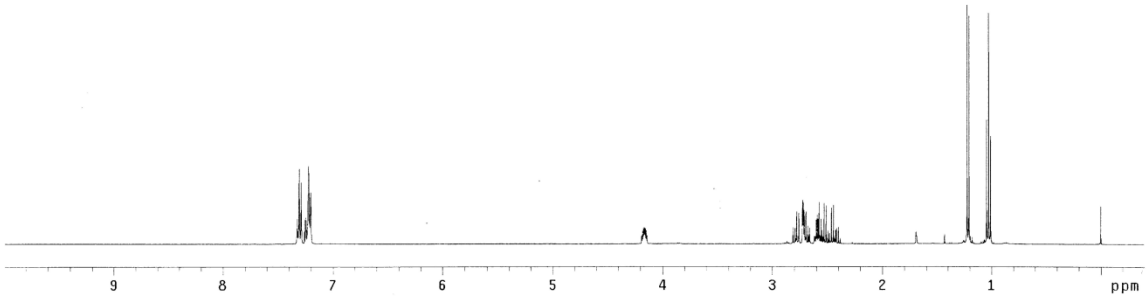


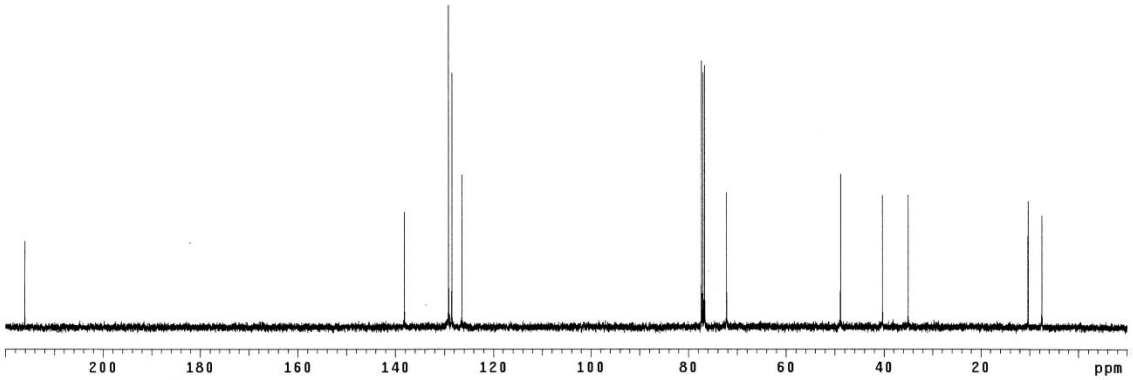




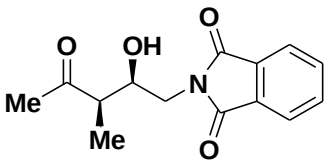
(4*R*,5*S*)-5-hydroxy-4-methyl-6-phenylhexan-3-one, 2.70a

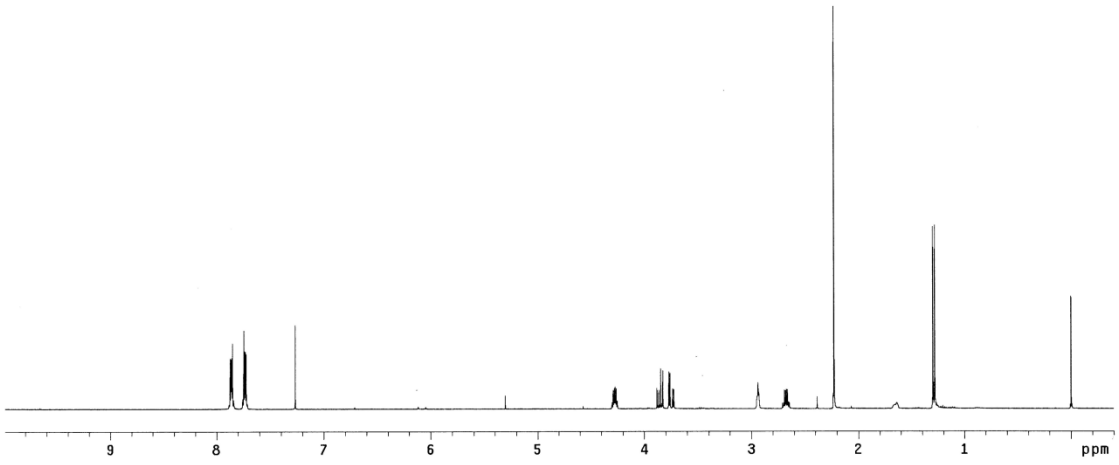


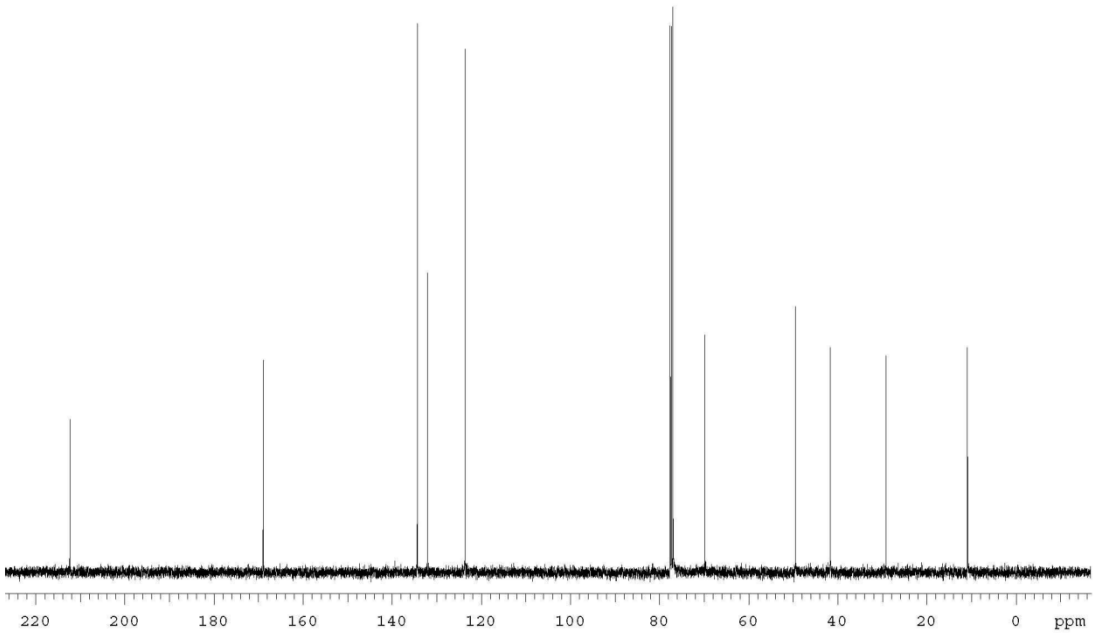




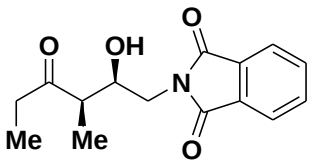
2-((2*R*,3*R*)-2-hydroxy-3-methyl-4-oxopentyl)isoindoline-1,3-dione, 2.56

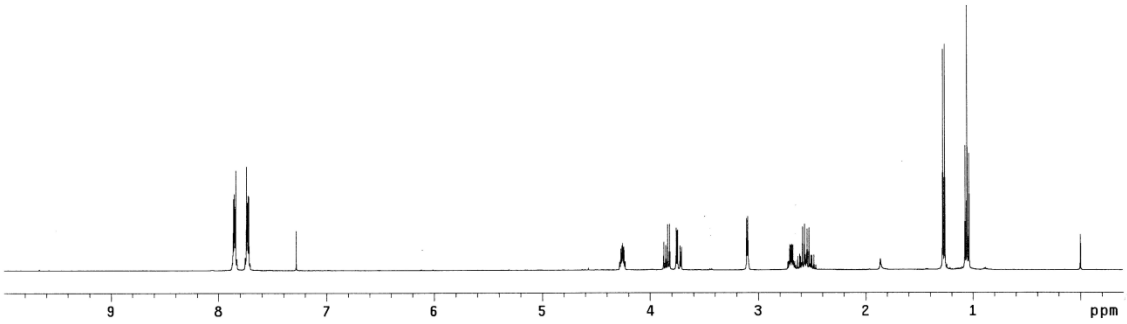


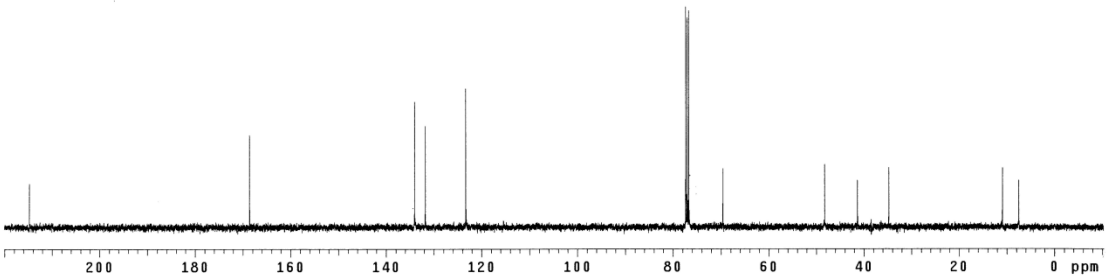




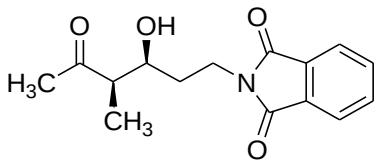
2-((2*R*,3*R*)-2-hydroxy-3-methyl-4-oxohexyl)isoindoline-1,3-dione, 2.56a

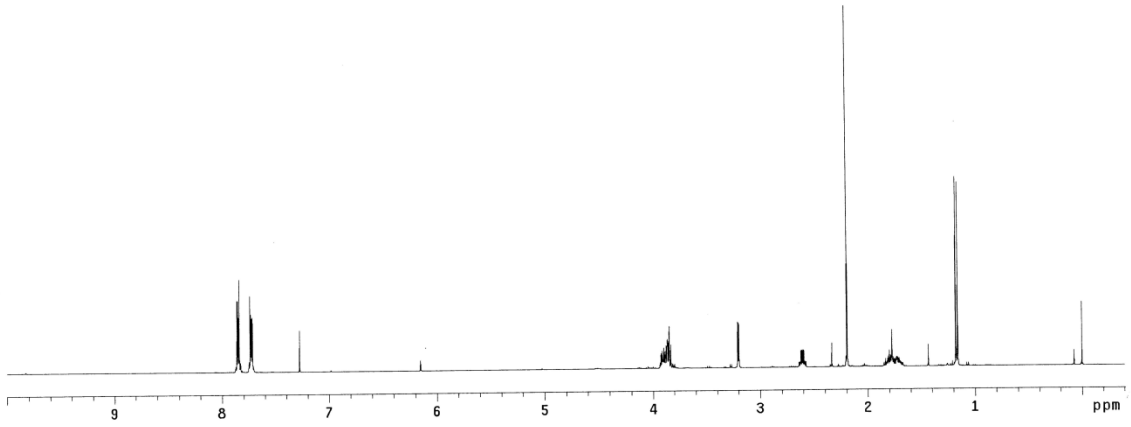


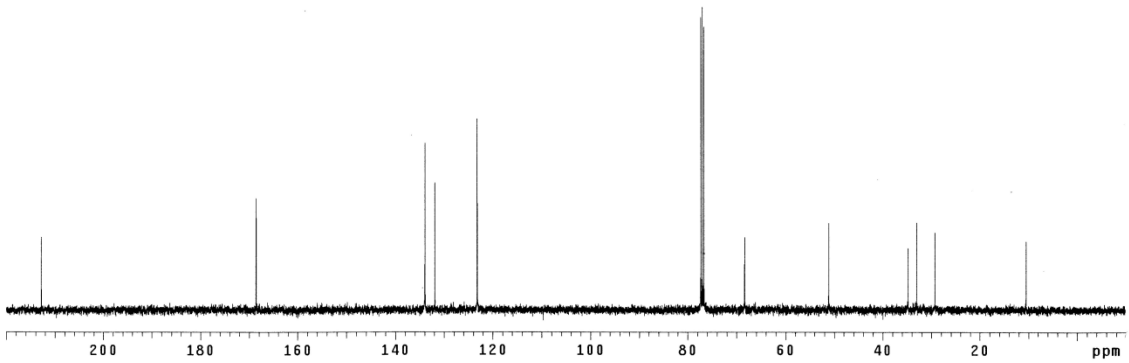




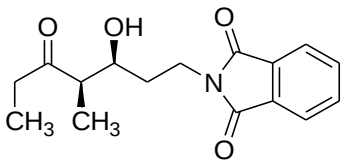
2-((3S,4R)-3-hydroxy-4-methyl-5-oxohexyl)isoindoline-1,3-dione, 2. 69

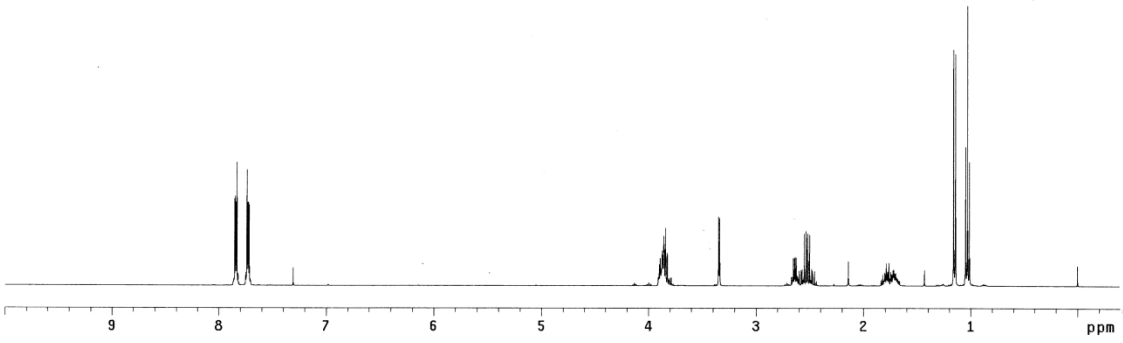


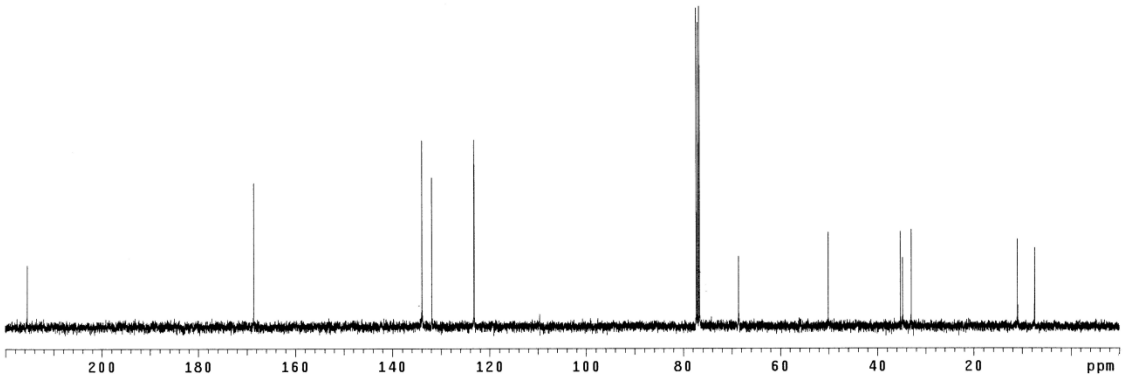




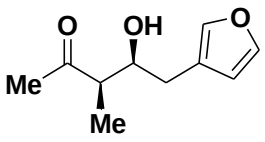
2-((3S,4R)-3-hydroxy-4-methyl-5-oxoheptyl)isoindoline-1,3-dione, 2.69a

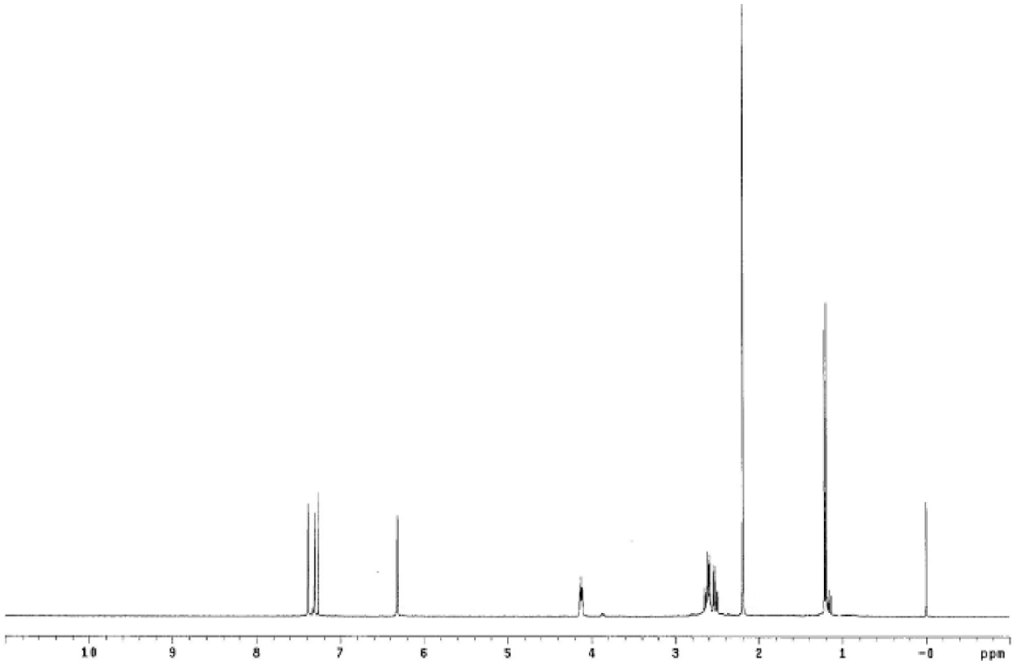


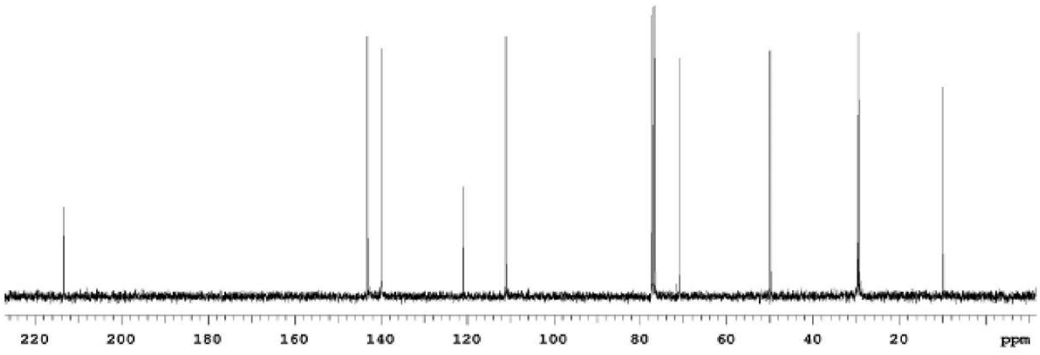




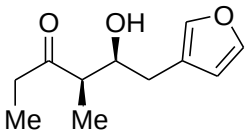
(3*R*,4*S*)-5-(furan-3-yl)-4-hydroxy-3-methylpentan-2-one, 2.72

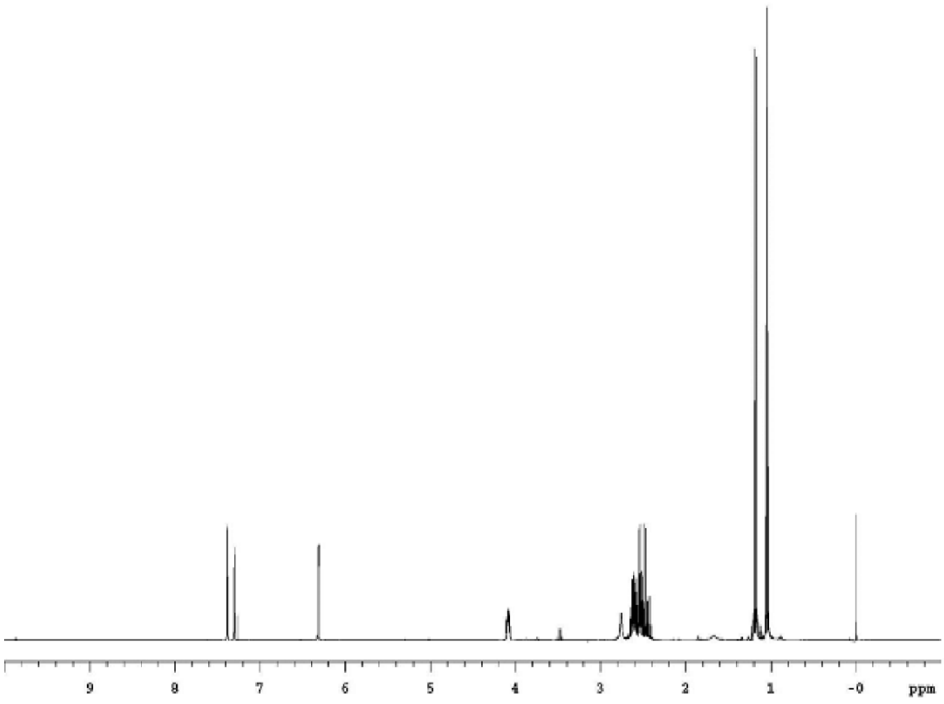


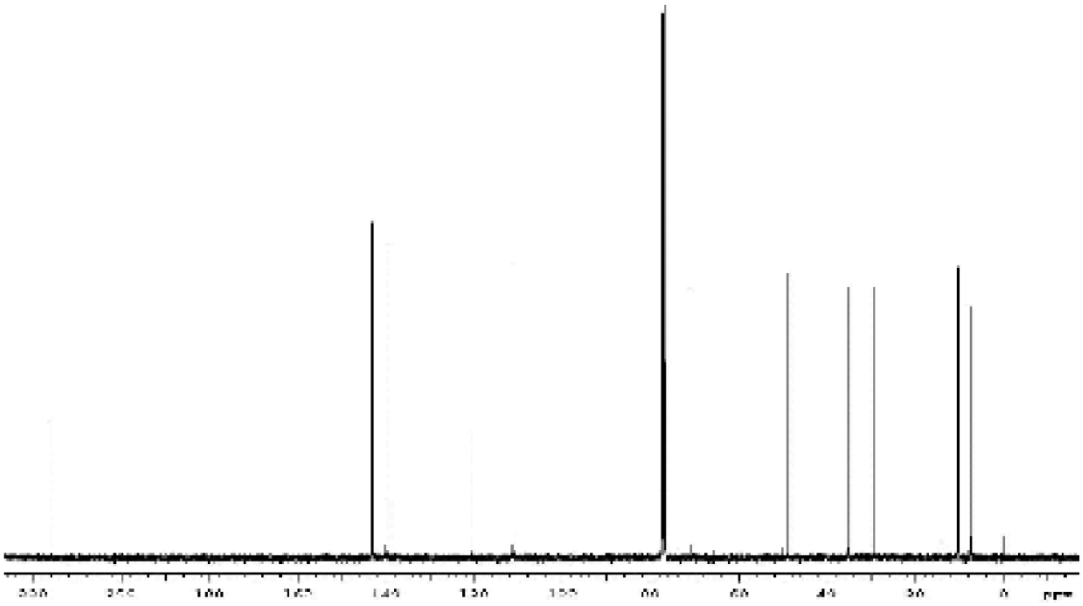




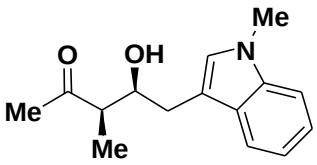
(4*R*,5*S*)-6-(furan-3-yl)-5-hydroxy-4-methylhexan-3-one, 2.72a

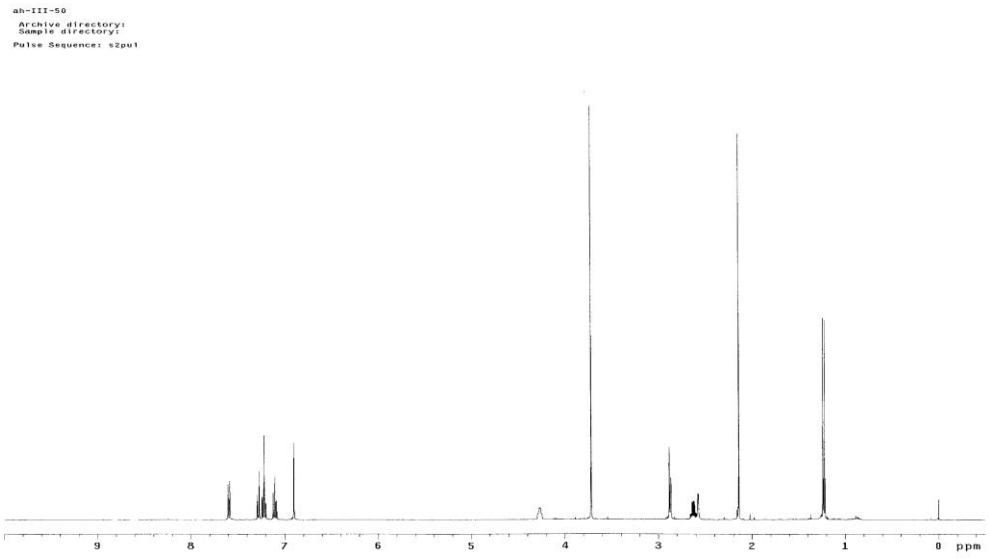


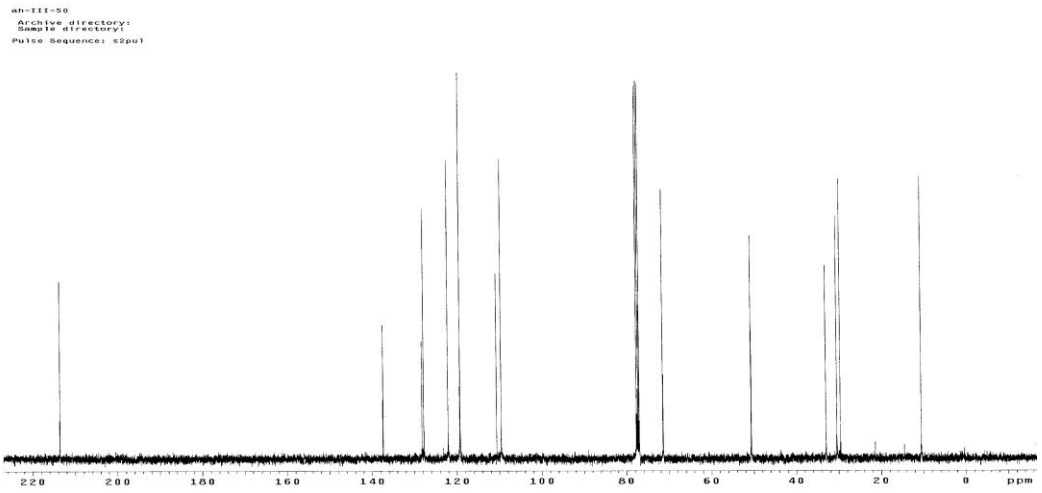




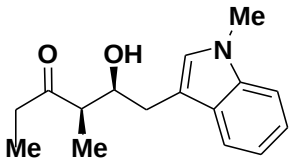
(3*R*,4*S*)-4-hydroxy-3-methyl-5-(1-methyl-1H-indol-3-yl)pentan-2-one, 2.71

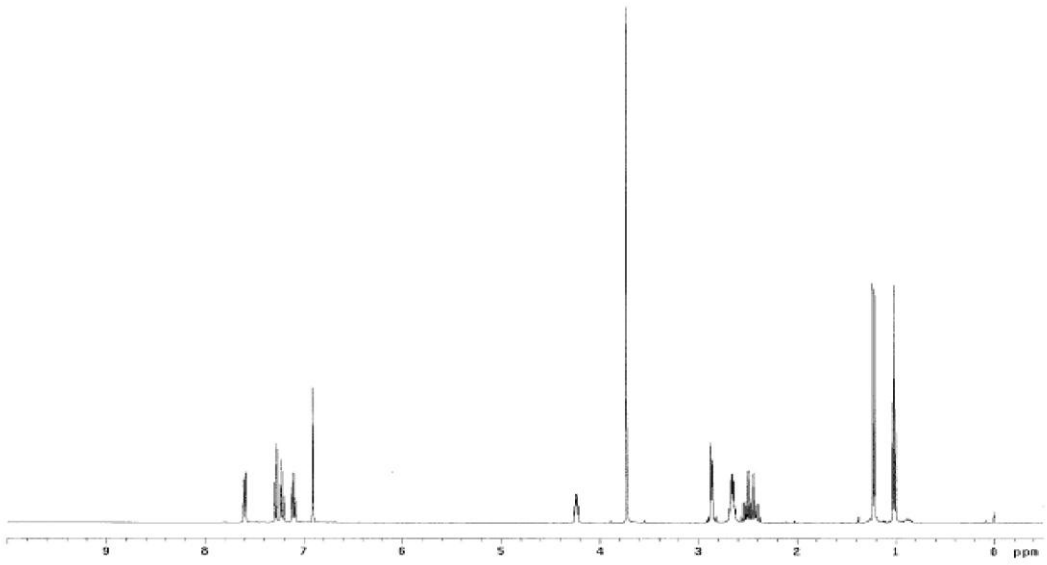


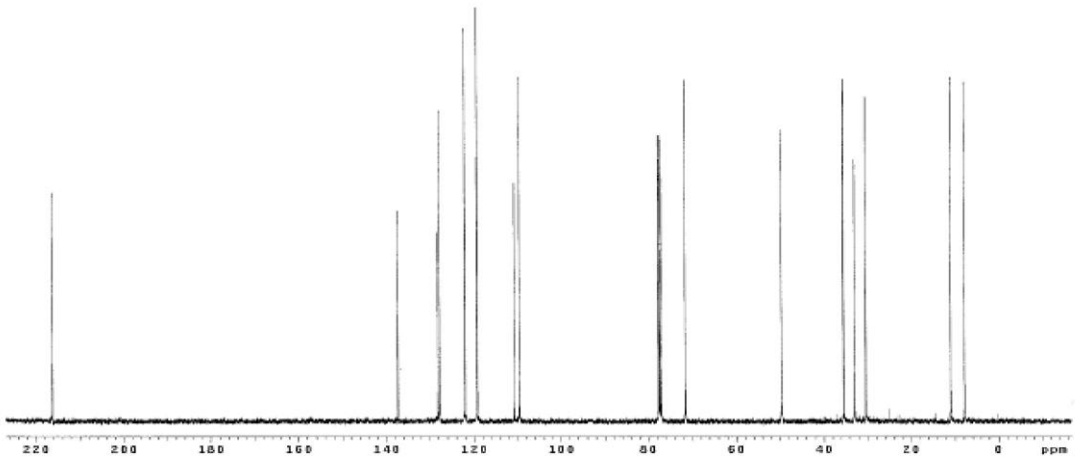




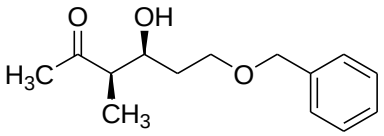
(4*R*,5*S*)-5-hydroxy-4-methyl-6-(1-methyl-1H-indol-3-yl)hexan-3-one, 2.71a

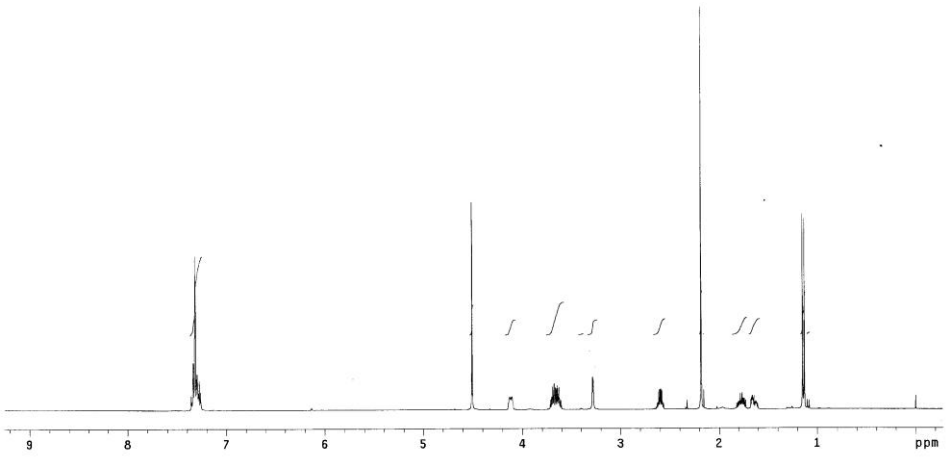


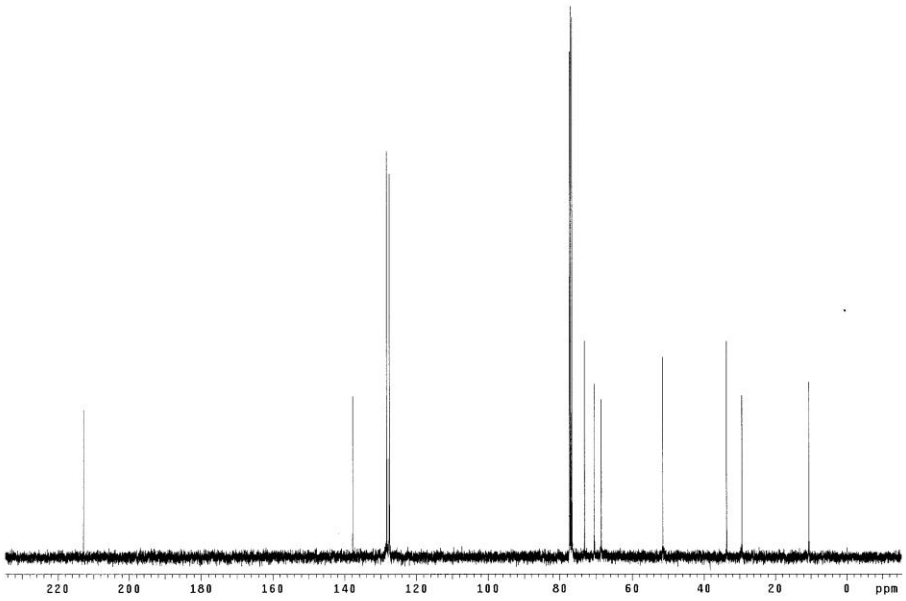




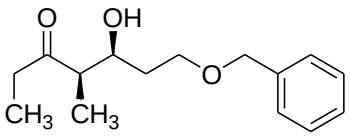
(3R,4S)-6-(benzyloxy)-4-hydroxy-3-methylhexan-2-one, 2.74

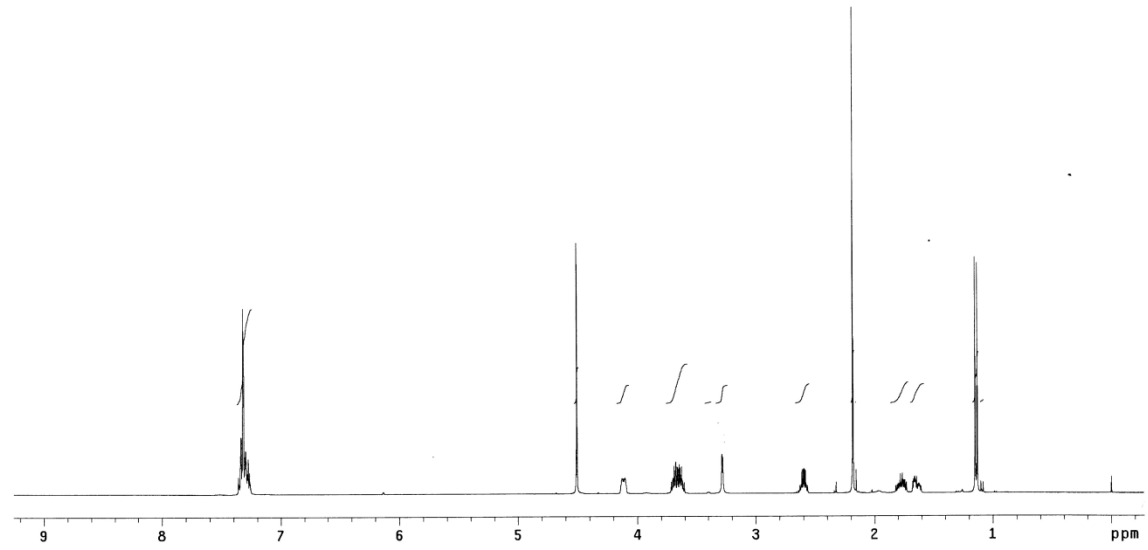


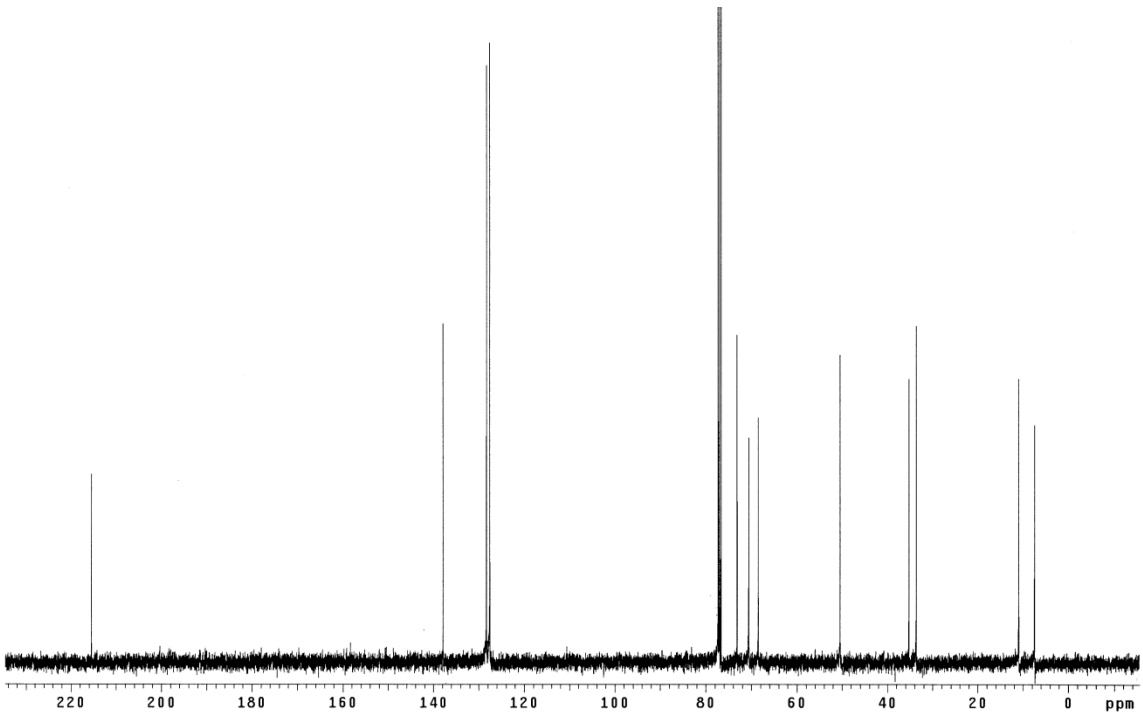




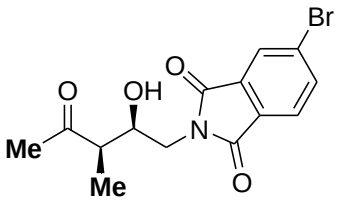
(4R,5S)-7-(benzyloxy)-5-hydroxy-4-methylheptan-3-one, 2.74a

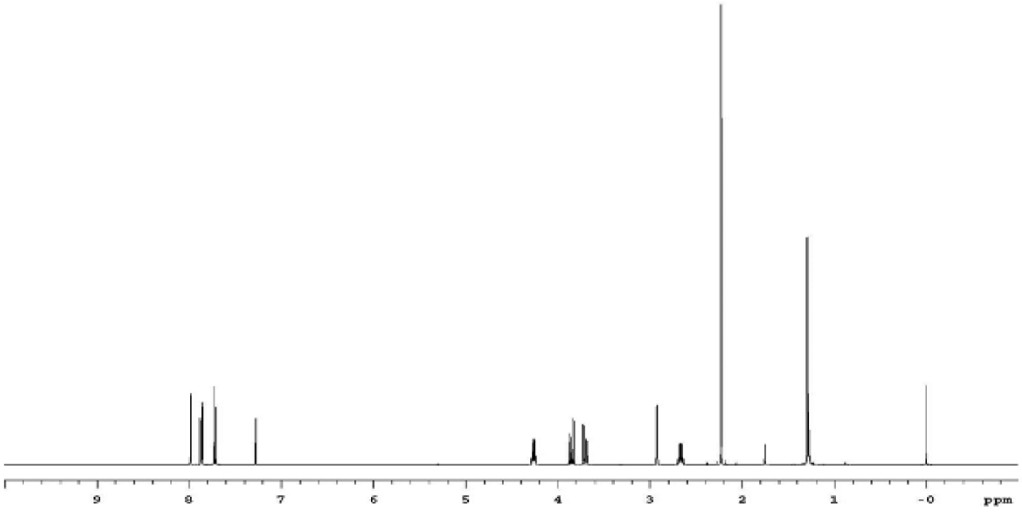


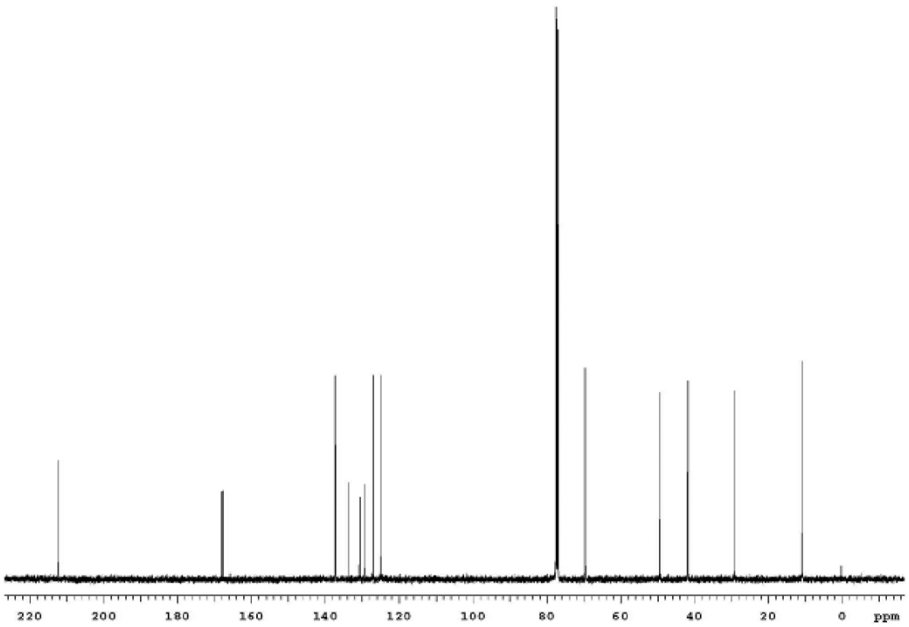




5-bromo-2-((2*R*,3*R*)-2-hydroxy-3-methyl-4-oxopentyl)isoindoline-1,3-dione, 2.75



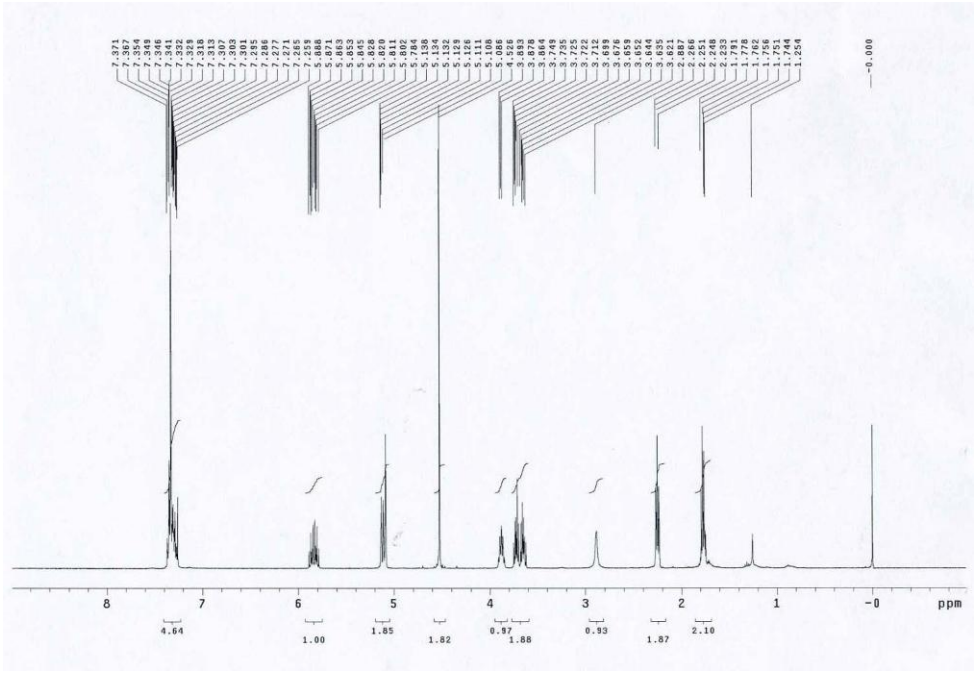


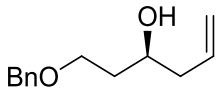


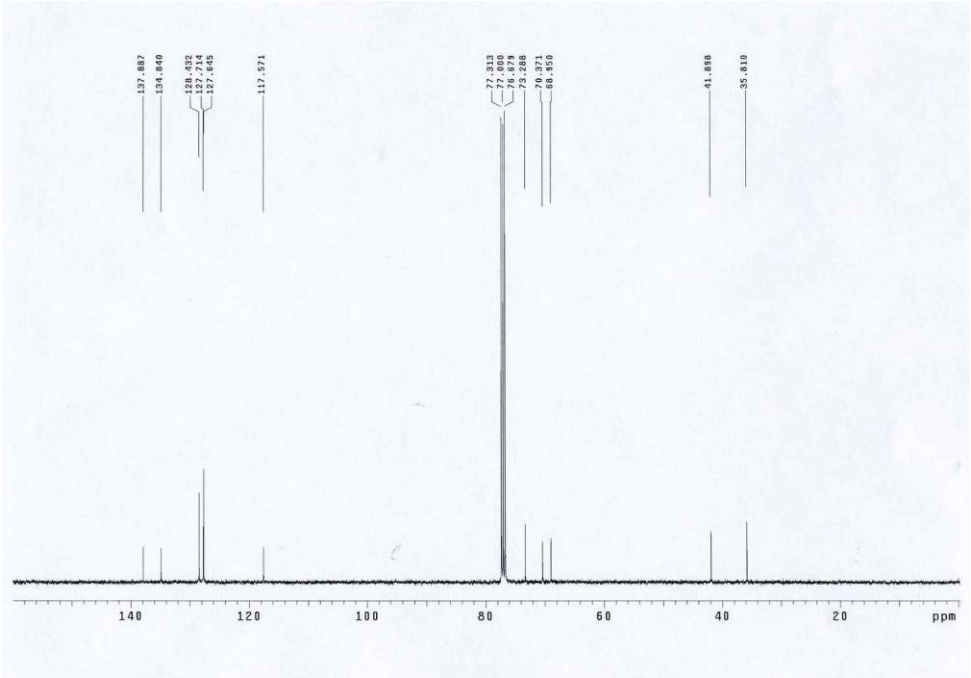
Chapter 3

I Part One: Elongation of 1,3-Polyol

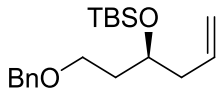
(*S*)-1-(Benzyloxy)hex-5-en-3-ol (3.5)

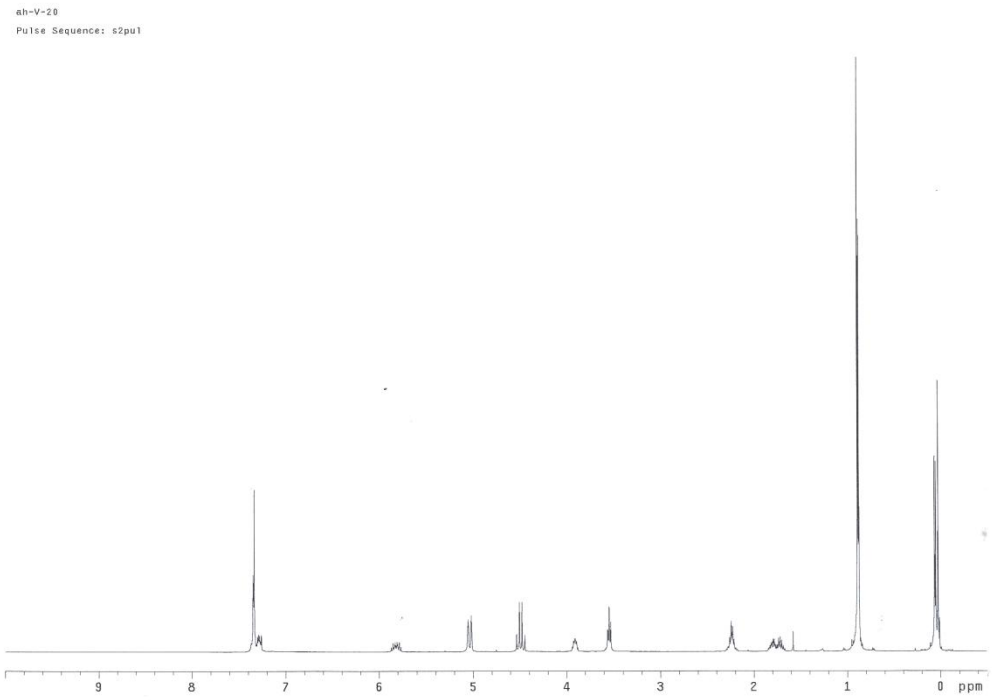


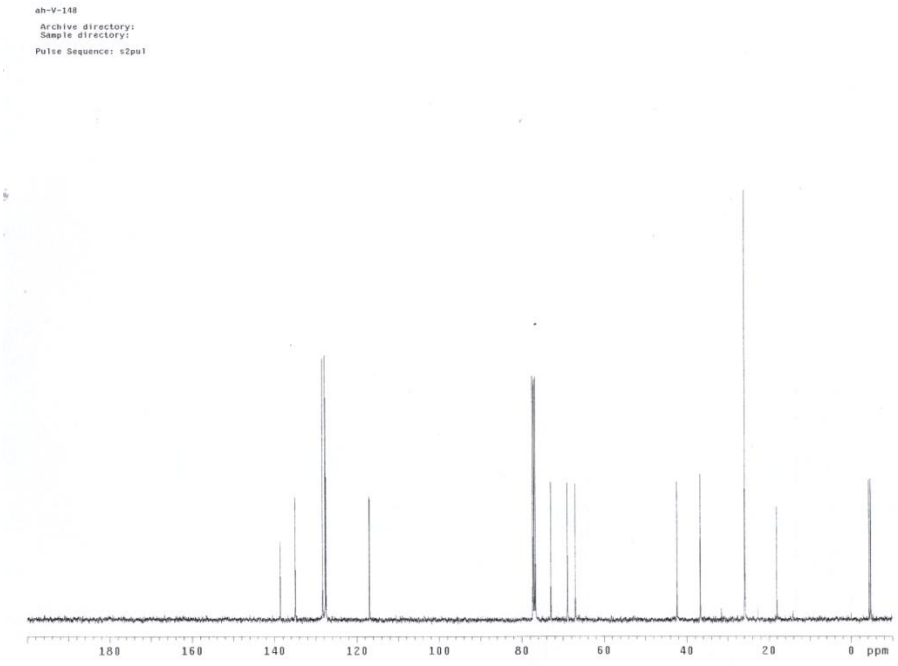




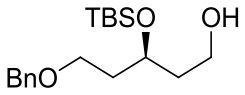
(*S*)-(1-(Benzyloxy)hex-5-en-3-yloxy)(tert-butyl)dimethylsilane (3.6)

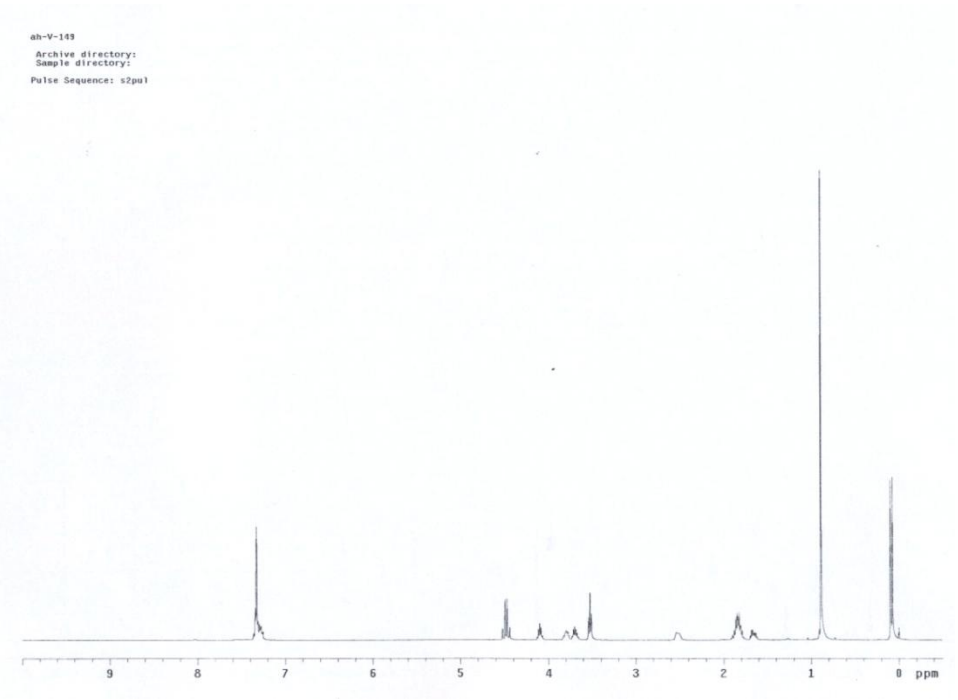


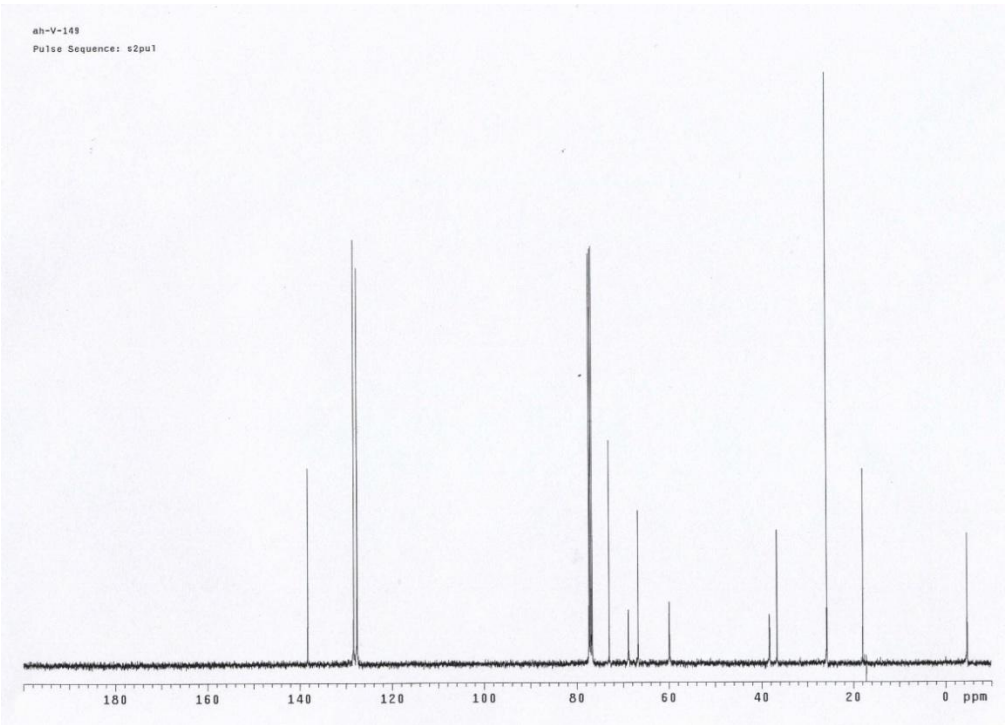




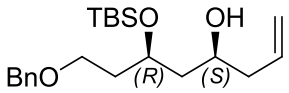
(*S*)-5-(Benzyloxy)-3-(tert-butyldimethylsilyloxy)pentan-1-ol (3.7)

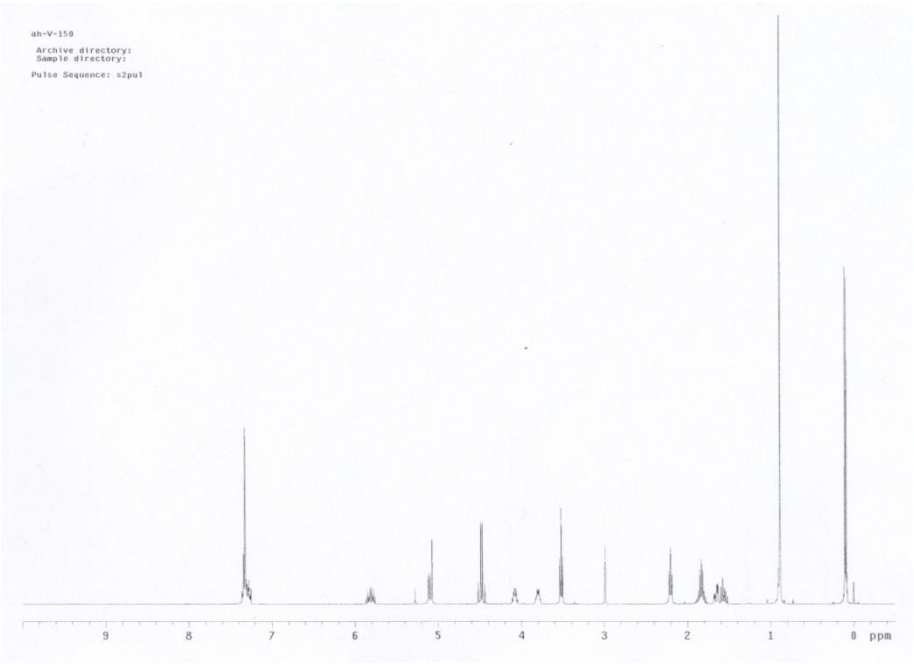


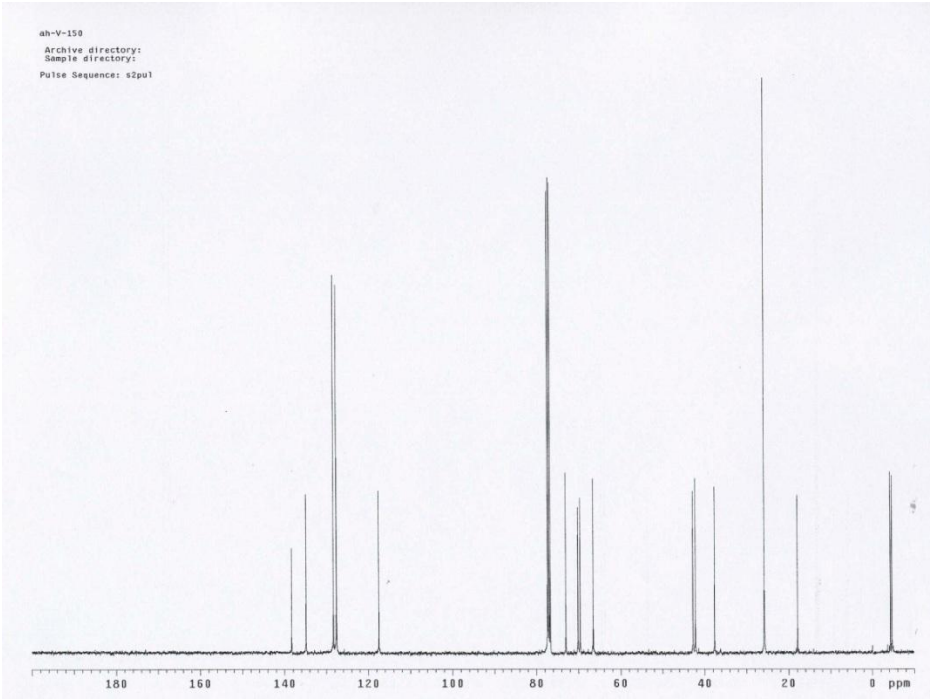




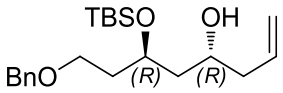
(4*S*,6*R*)-8-(Benzyloxy)-6-(tert-butyldimethylsilyloxy)oct-1-en-4-ol ((*R*,*S*)-3.8)

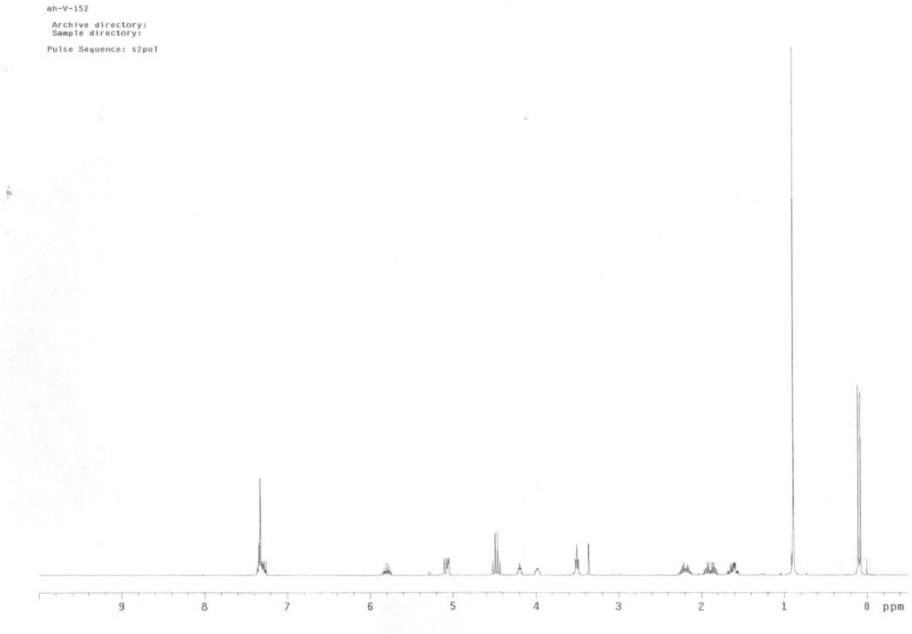


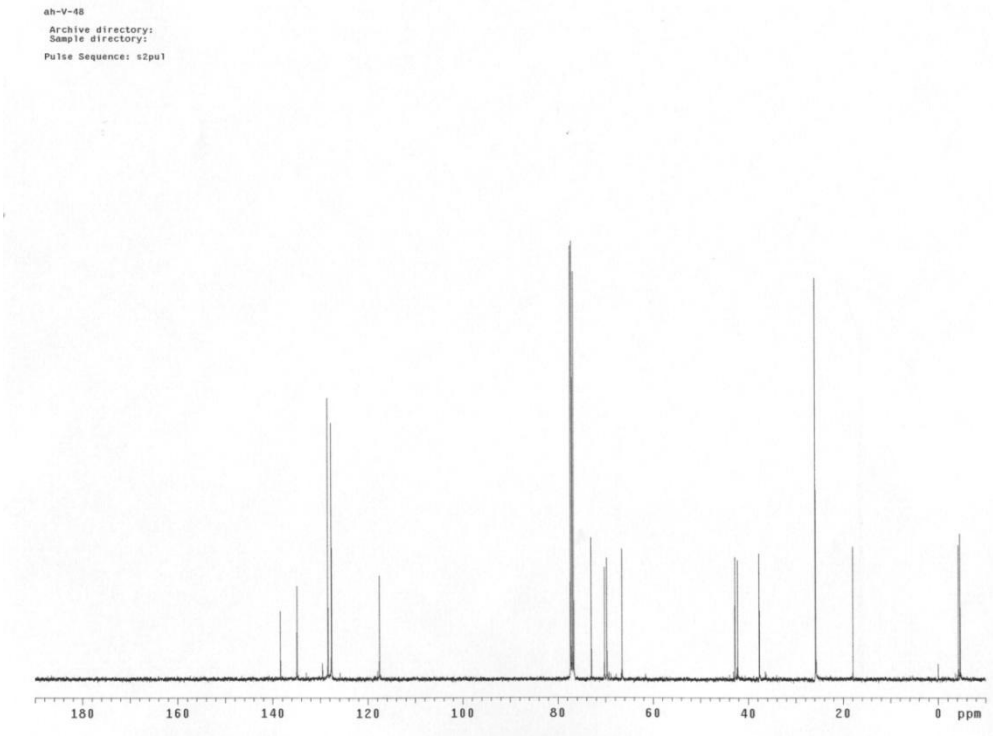




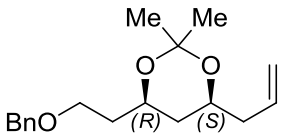
(4*R*,6*R*)-8-(Benzyloxy)-6-(tert-butyldimethylsilyloxy)oct-1-en-4-ol ((*R*,*R*)-3.8)

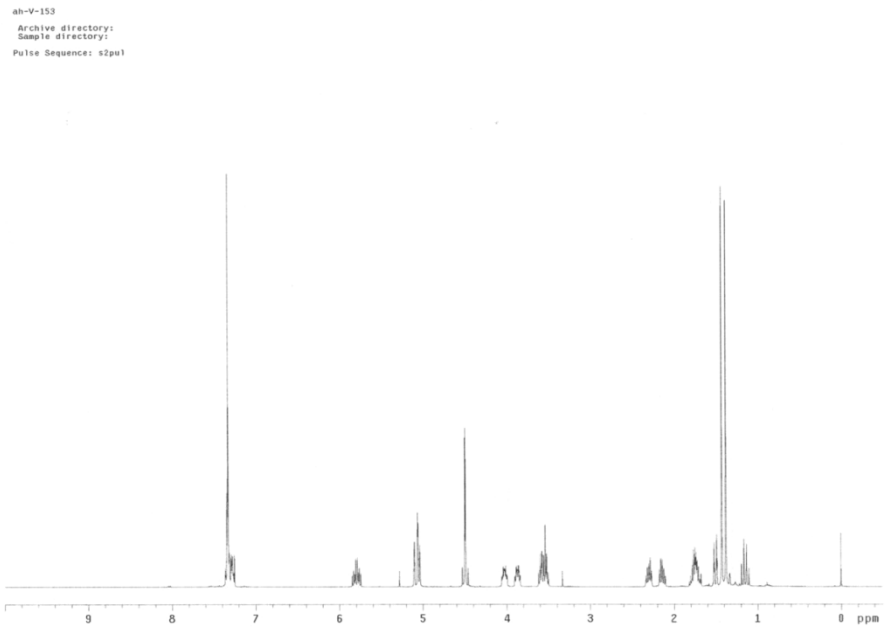


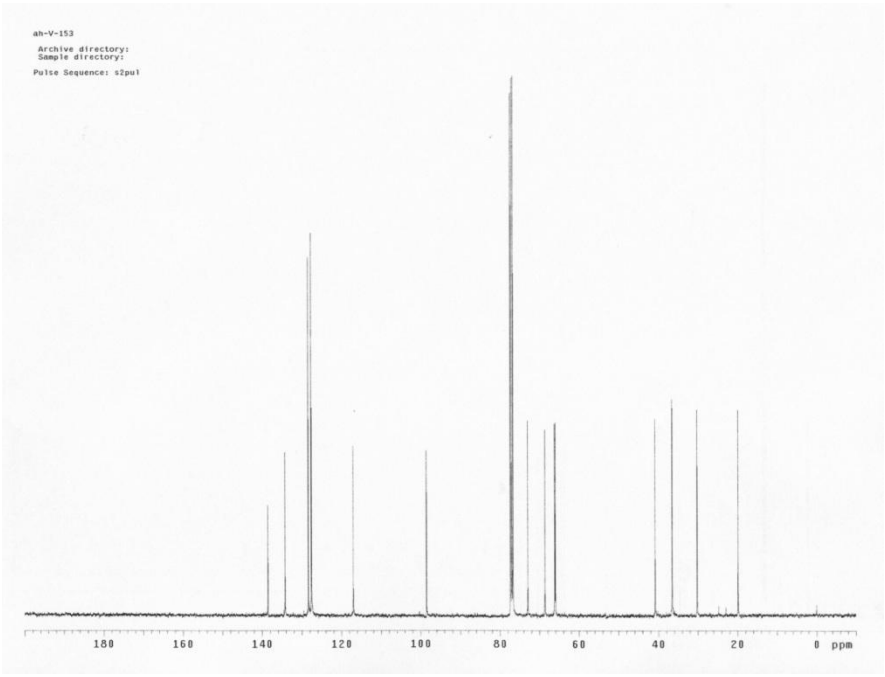




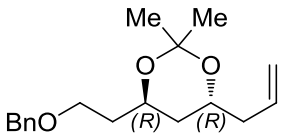
(4*S*,6*R*)-4-Allyl-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane ((*R*,*S*)-3.9)

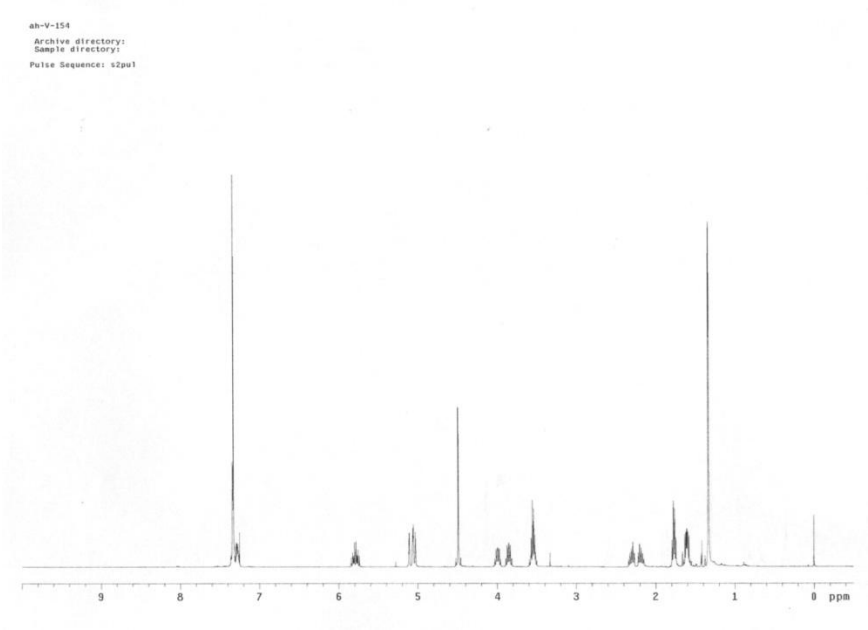


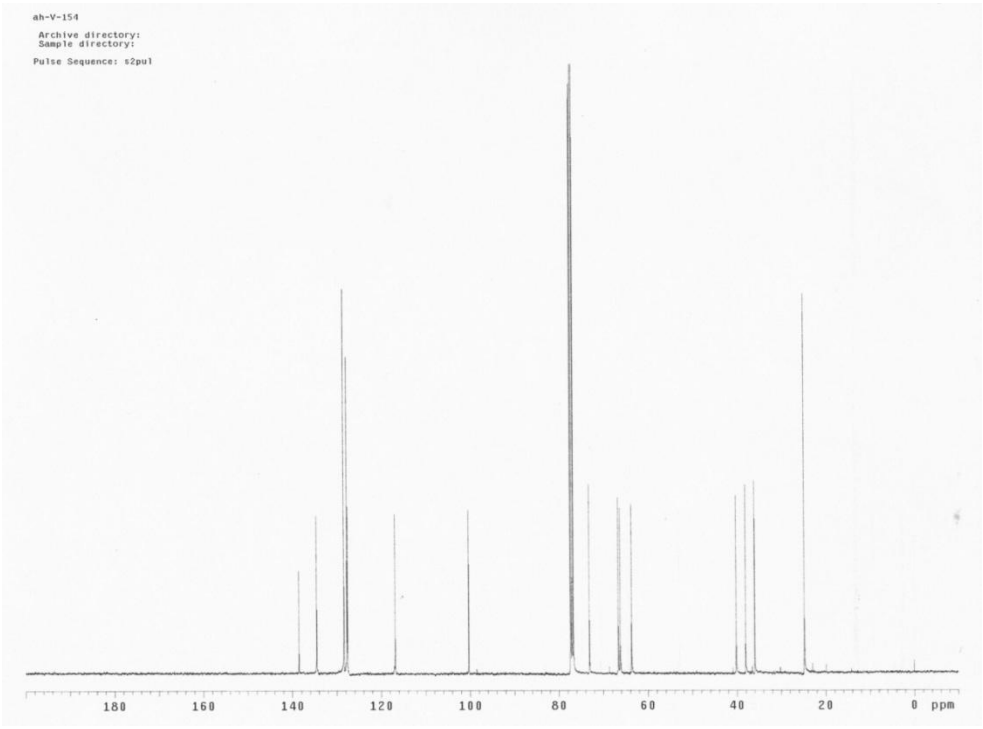




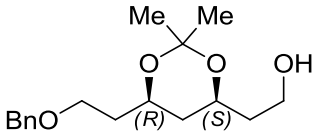
(4*R*,6*R*)-4-Allyl-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane ((*R*,*R*)-3.9)

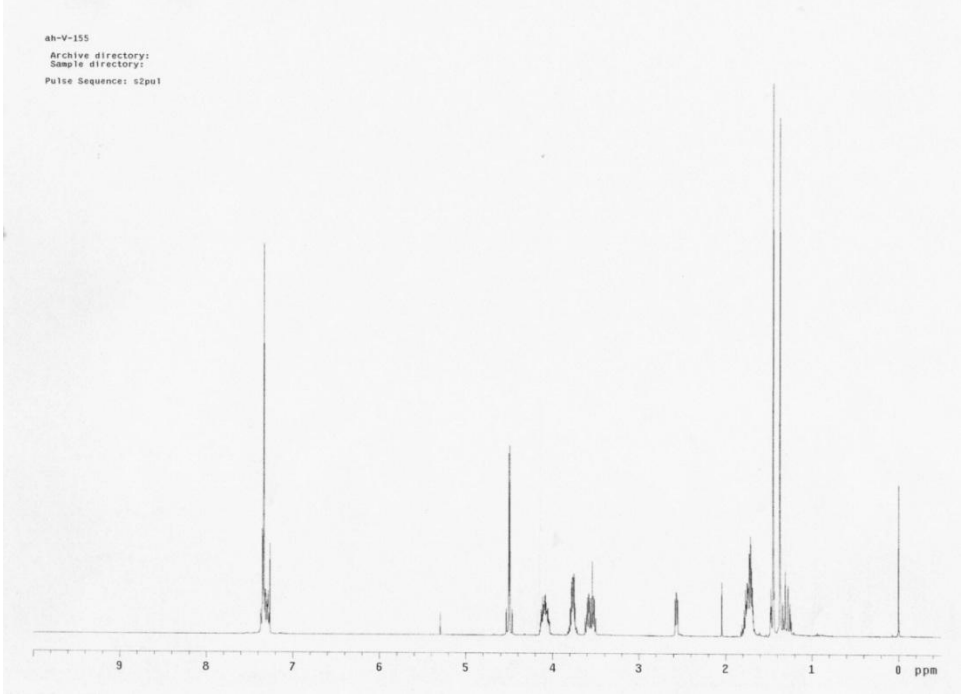


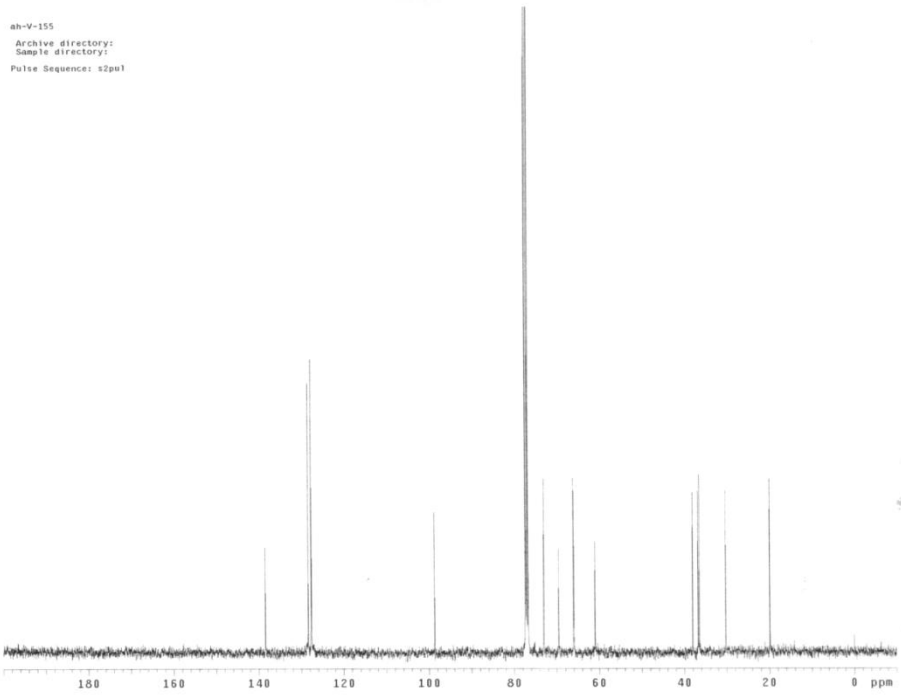




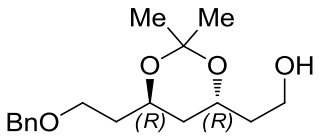
2-((4*S*,6*R*)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol ((*R*,*S*)-3.10)

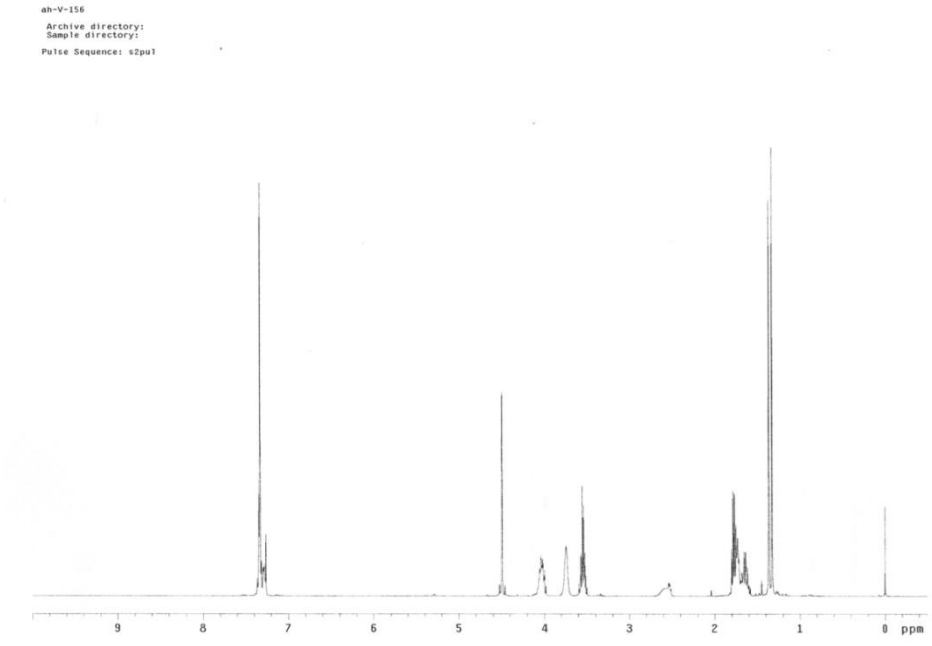


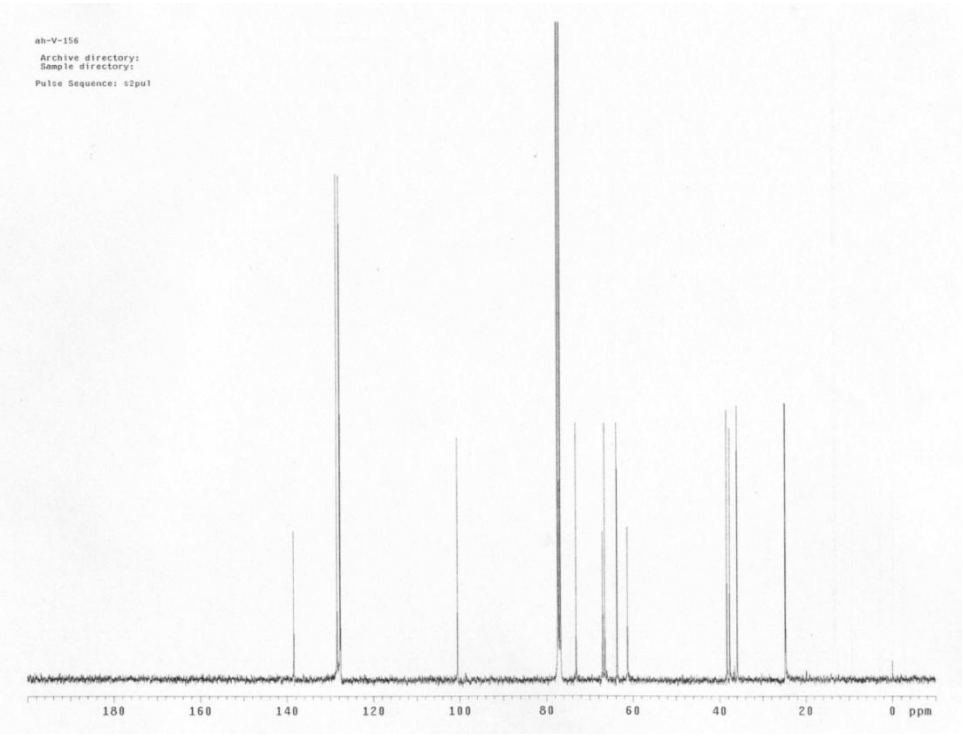




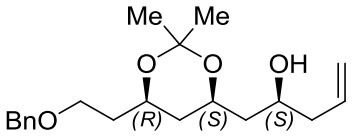
2-((4*R*,6*R*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol ((*R*,*R*)-3.10)

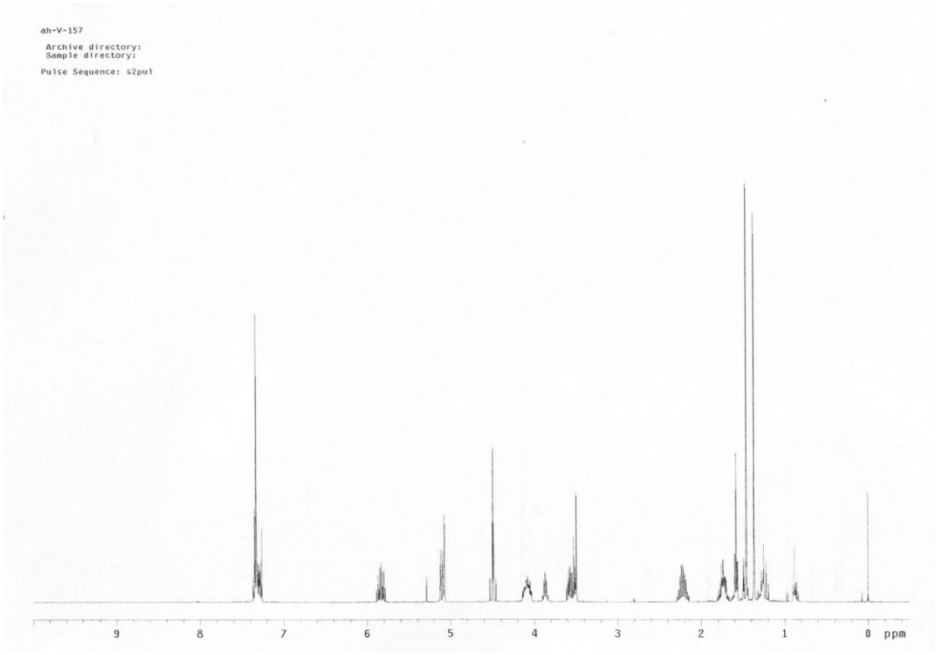


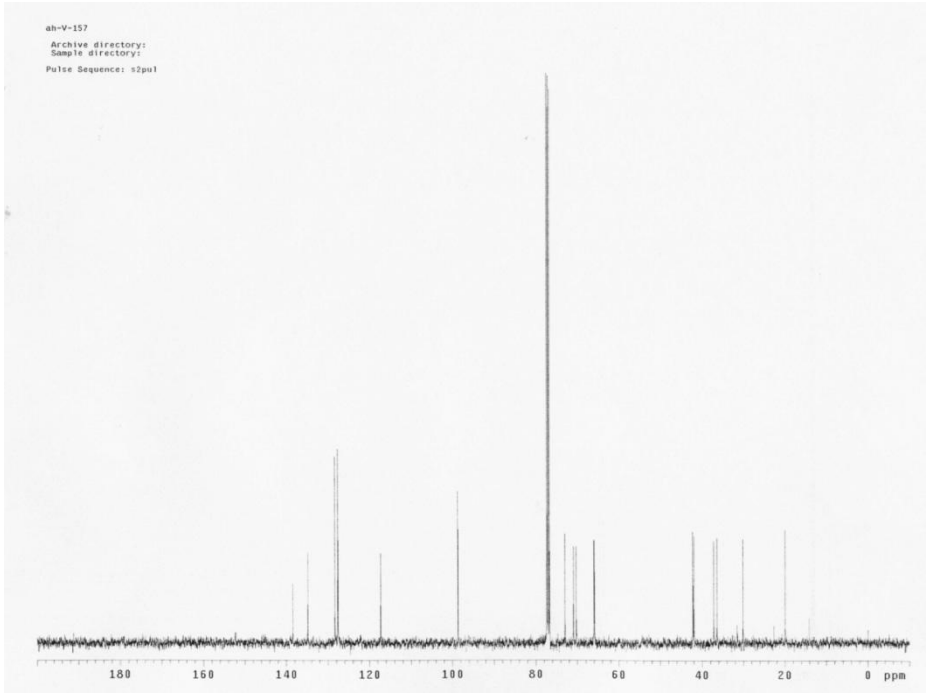




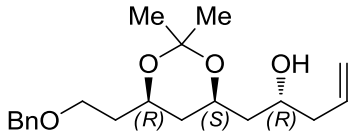
(*S*)-1-((4*S*,6*R*)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)pent-4-en-2-ol ((*R*,*S*,*S*)-3.11)

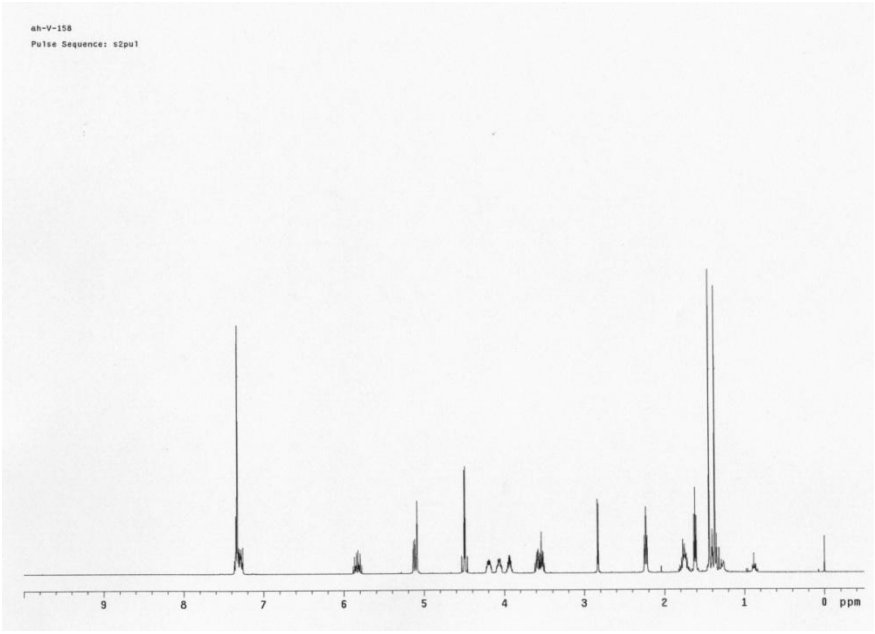


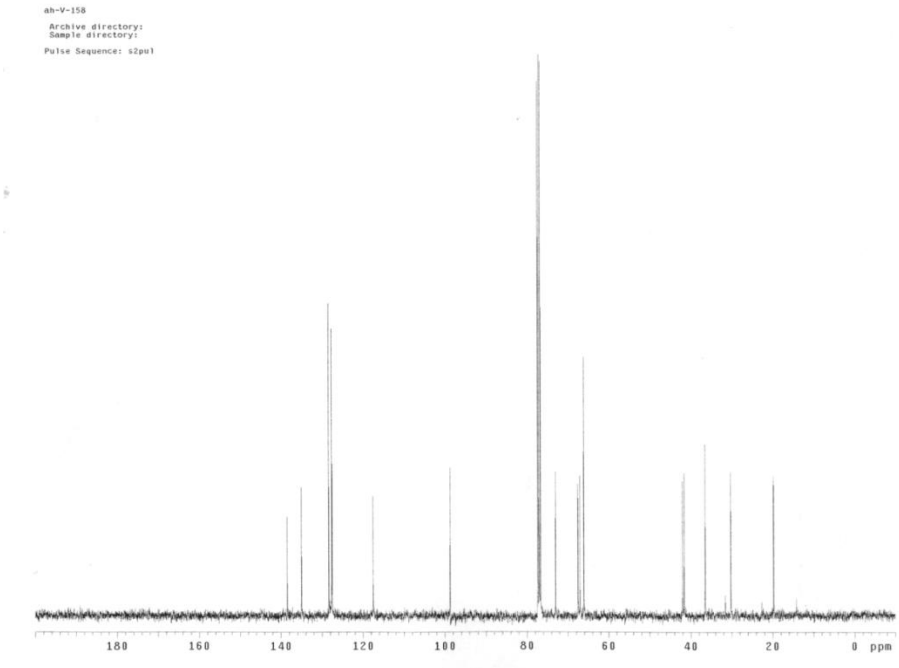




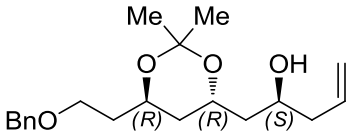
(*R*)-1-((4*S*,6*R*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)pent-4-en-2-ol ((*R*,*S*,*R*)-3.11)

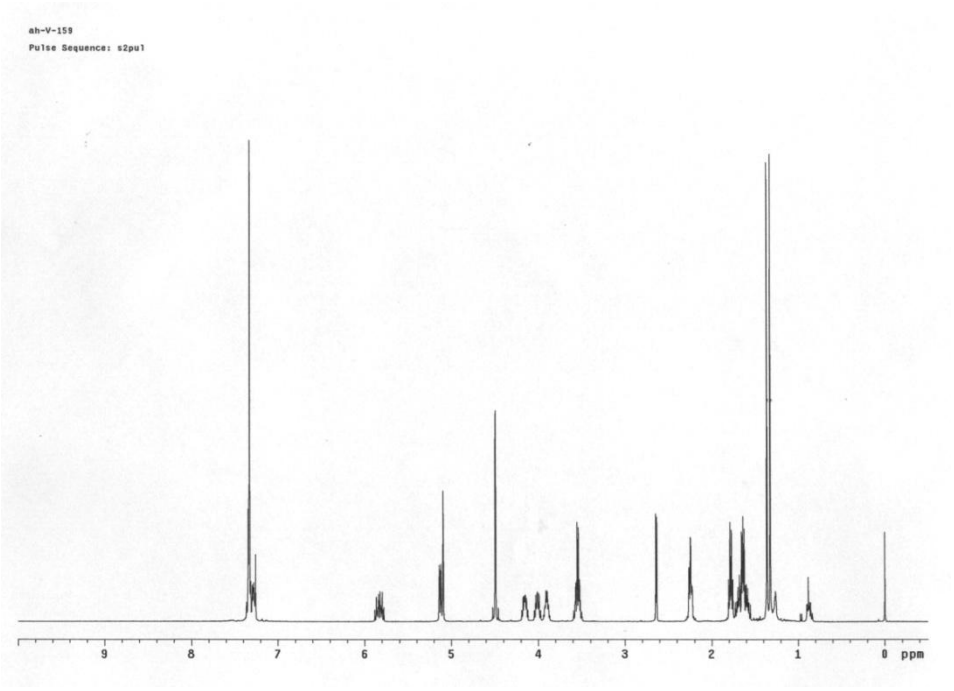


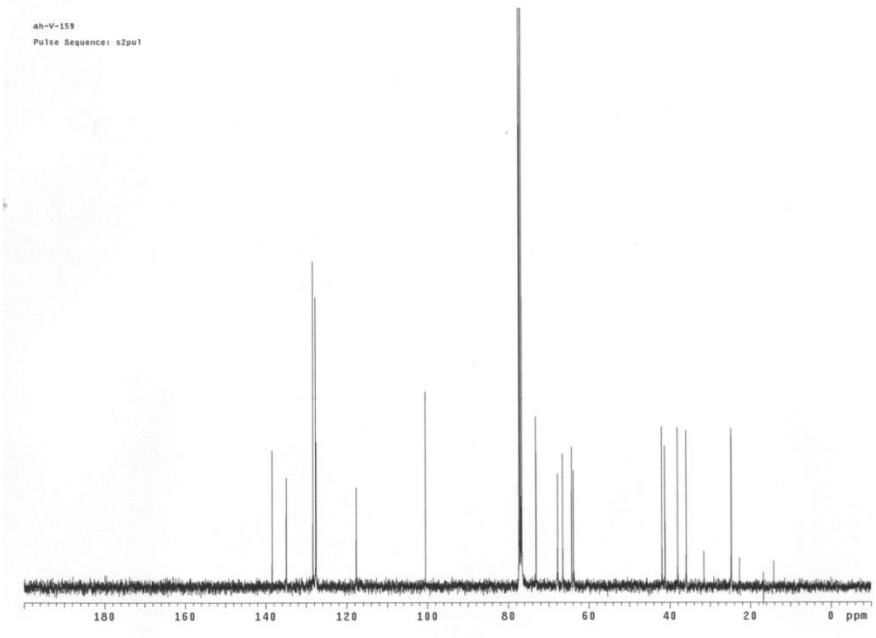




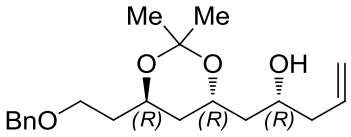
(*S*)-1-((4*R*,6*R*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)pent-4-en-2-ol ((*R*,*R*,*S*)-3.11)

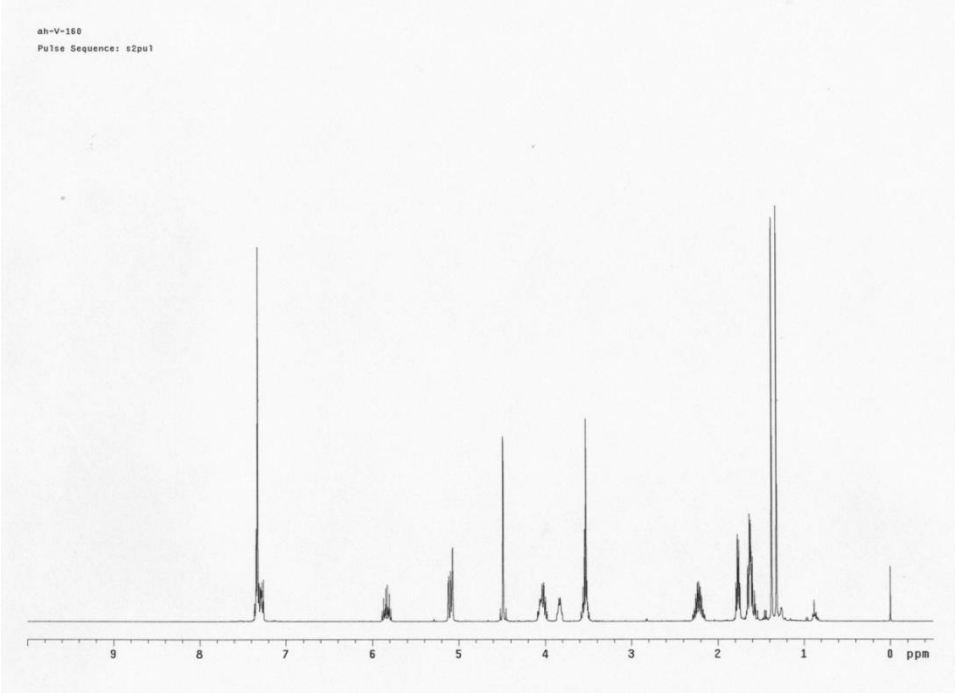


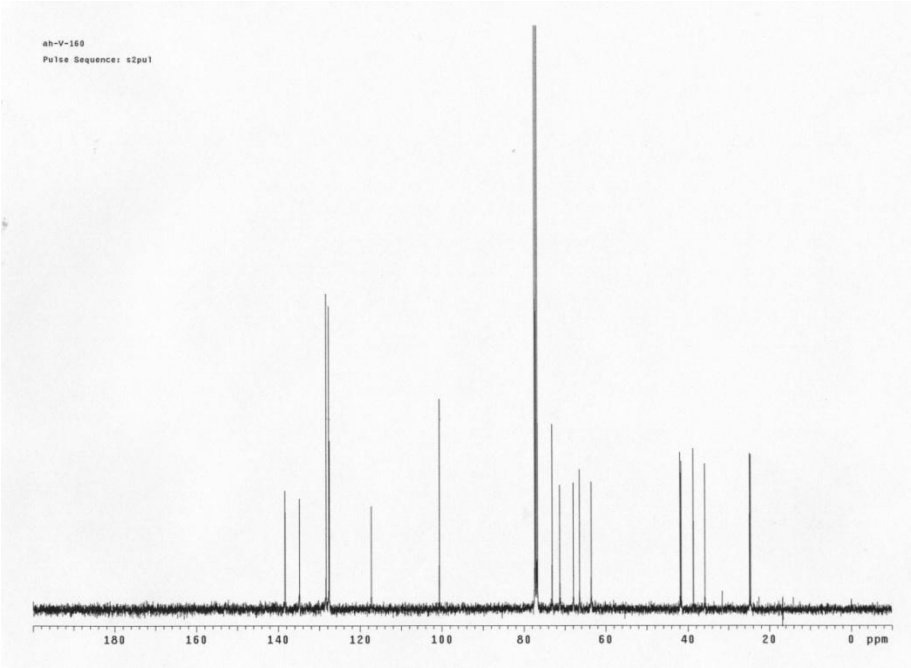




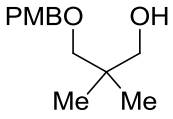
(*R*)-1-((4*R*,6*R*)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)pent-4-en-2-ol ((*R*,*R*,*R*)-3.11)

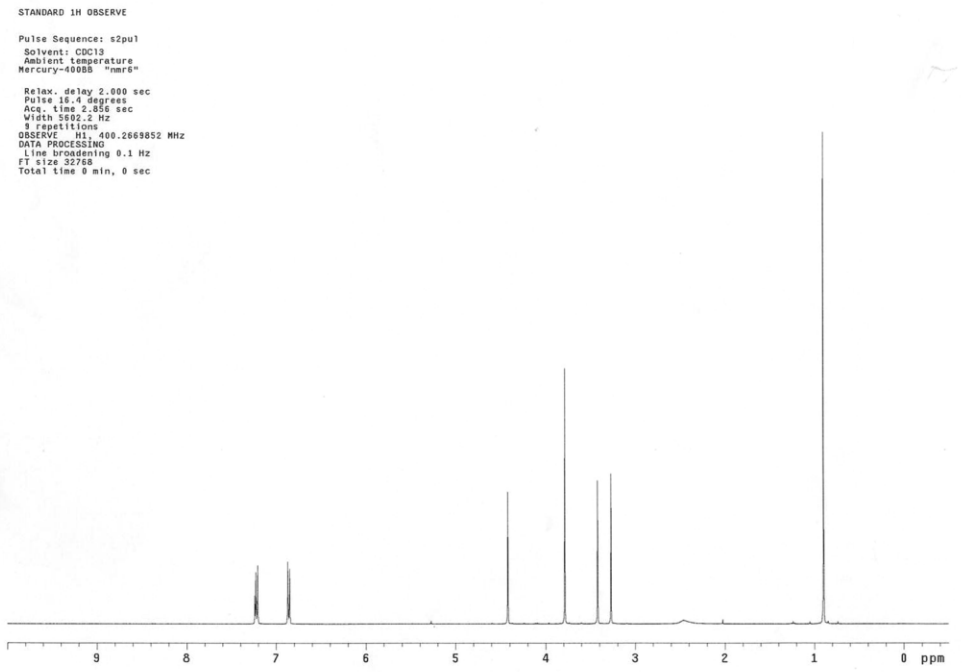


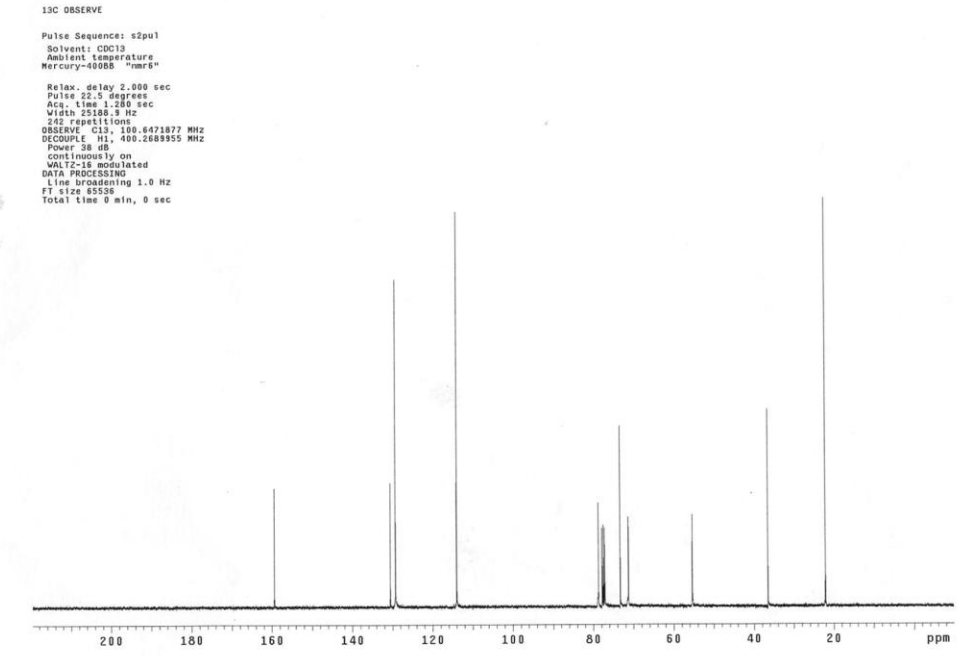




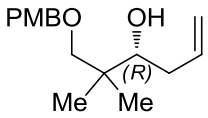
3-(4-Methoxybenzyloxy)-2,2-dimethylpropan-1-ol (3.12)

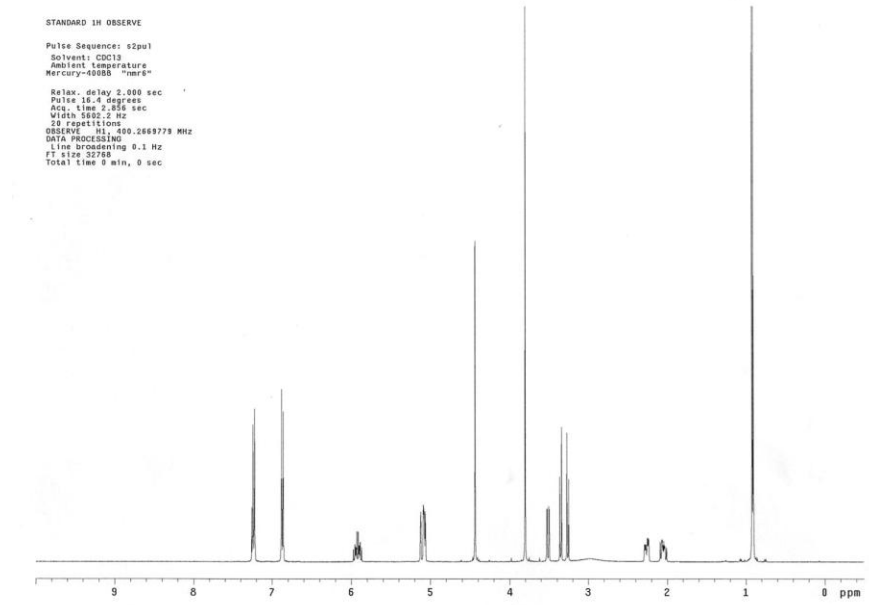


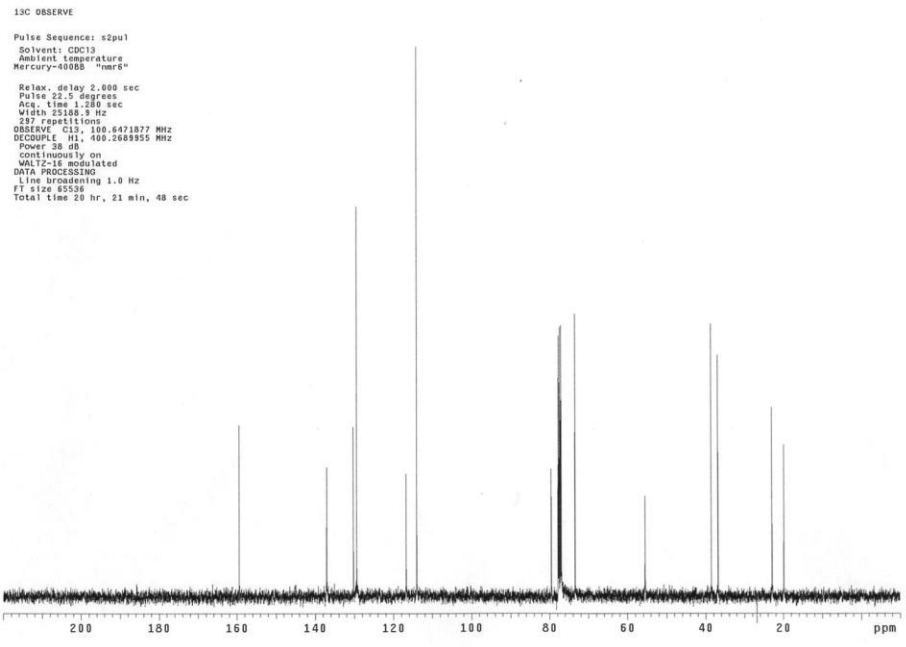




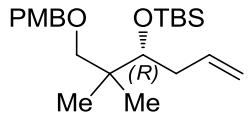
(R)-1-(4-Methoxybenzyloxy)-2,2-dimethylhex-5-en-3-ol (3.13)

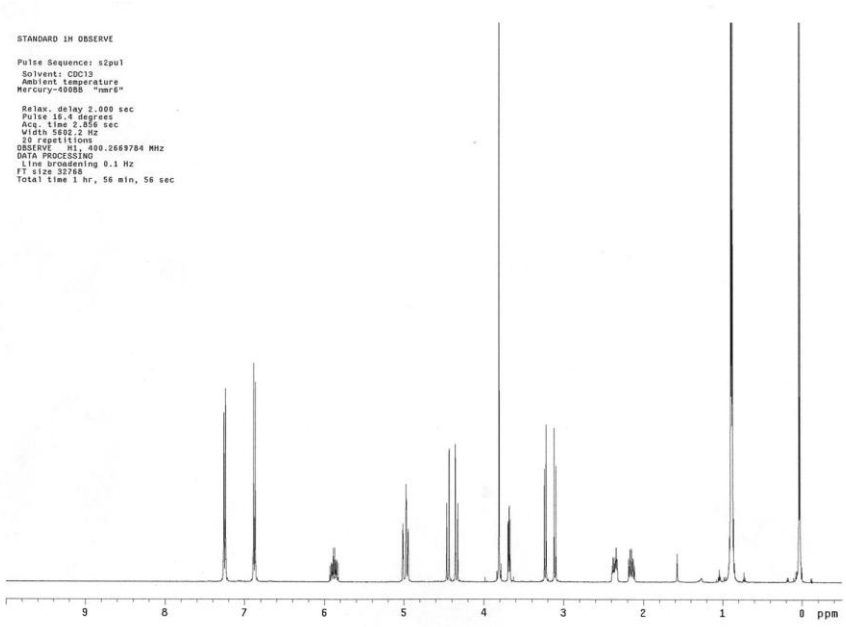


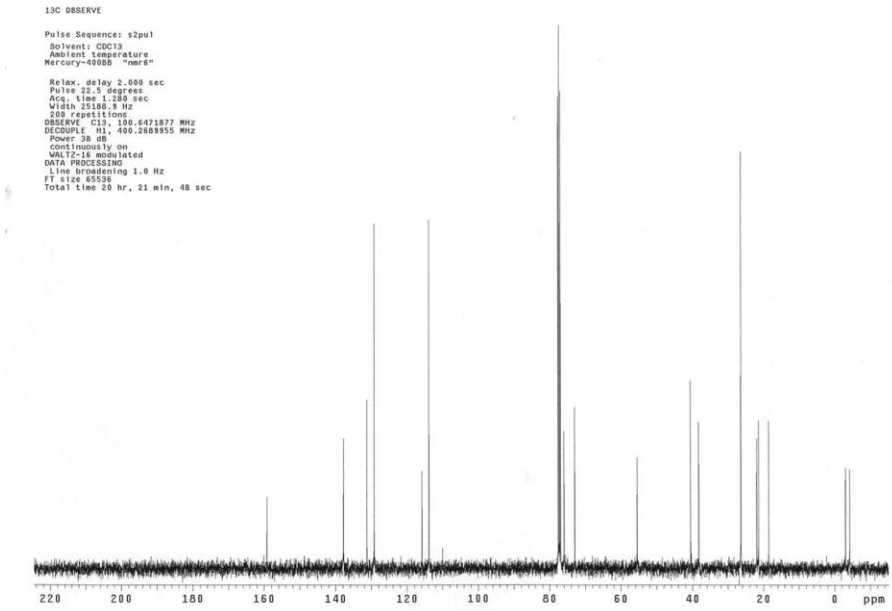




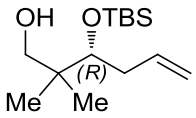
(*R*)-(1-(4-Methoxybenzyloxy)-2,2-dimethylhex-5-en-3-yloxy)(*tert*-butyl)dimethylsilane (3.13a)

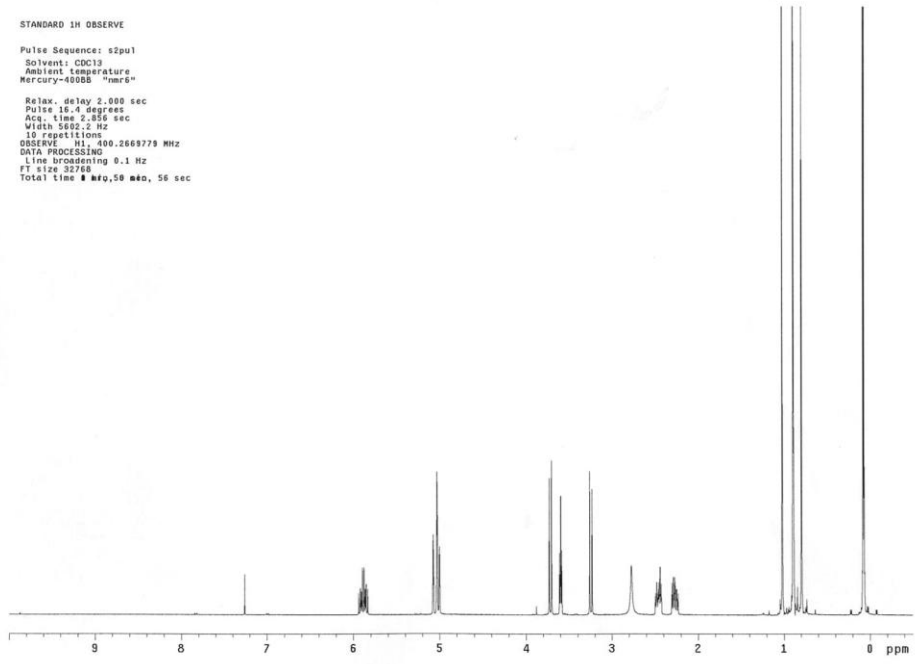


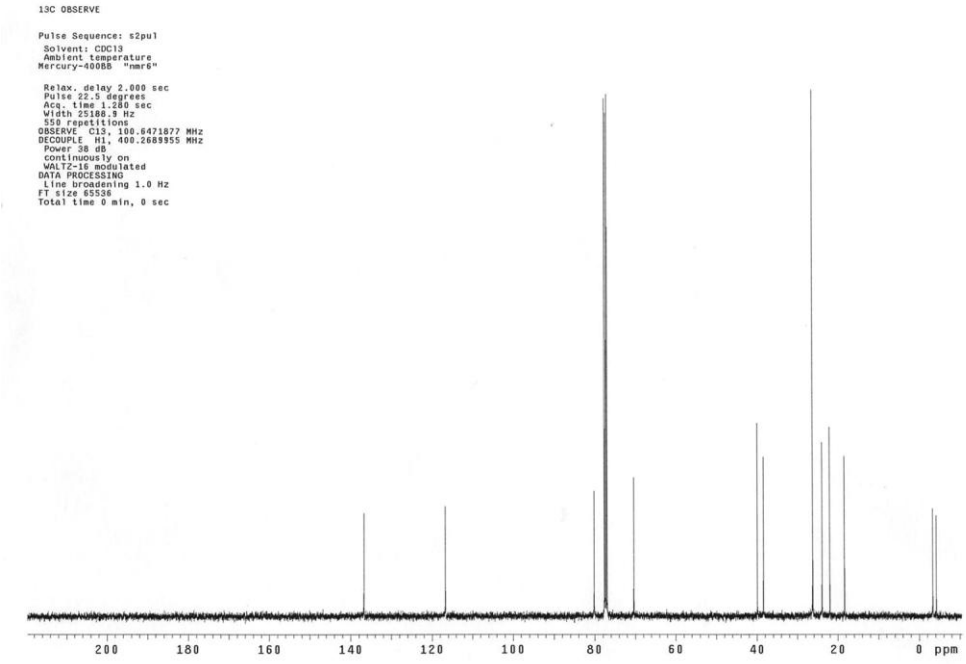




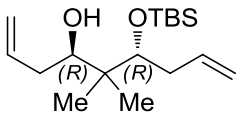
(*R*)-3-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylhex-5-en-l-ol (3.14)

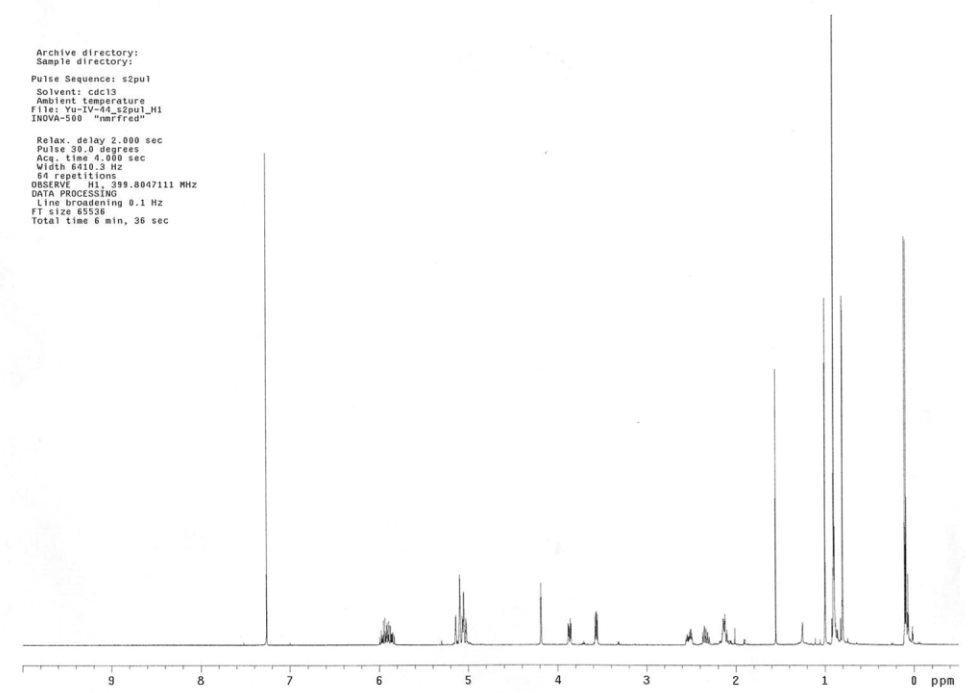


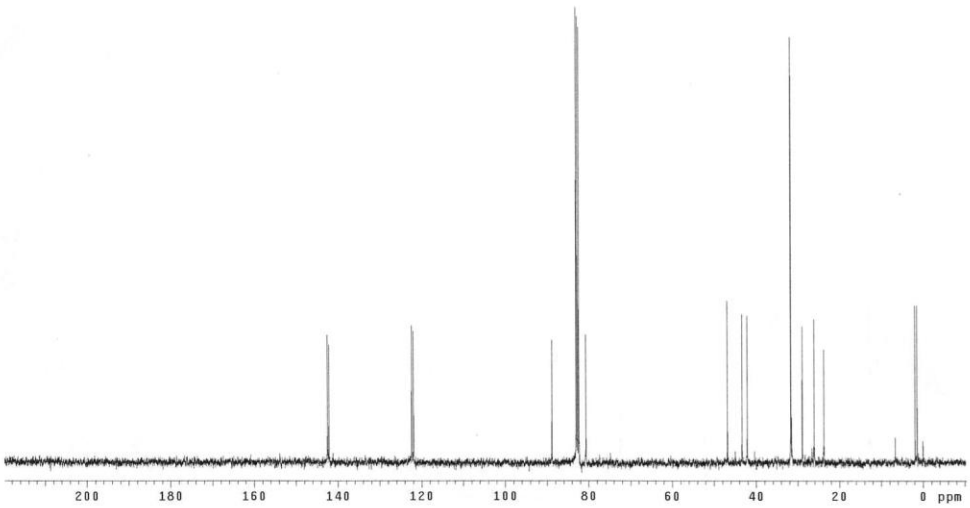




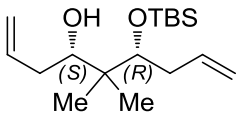
(4*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-5,5-dimethylnona-l,8-dien-4-ol ((*R*,*R*)-3.15)

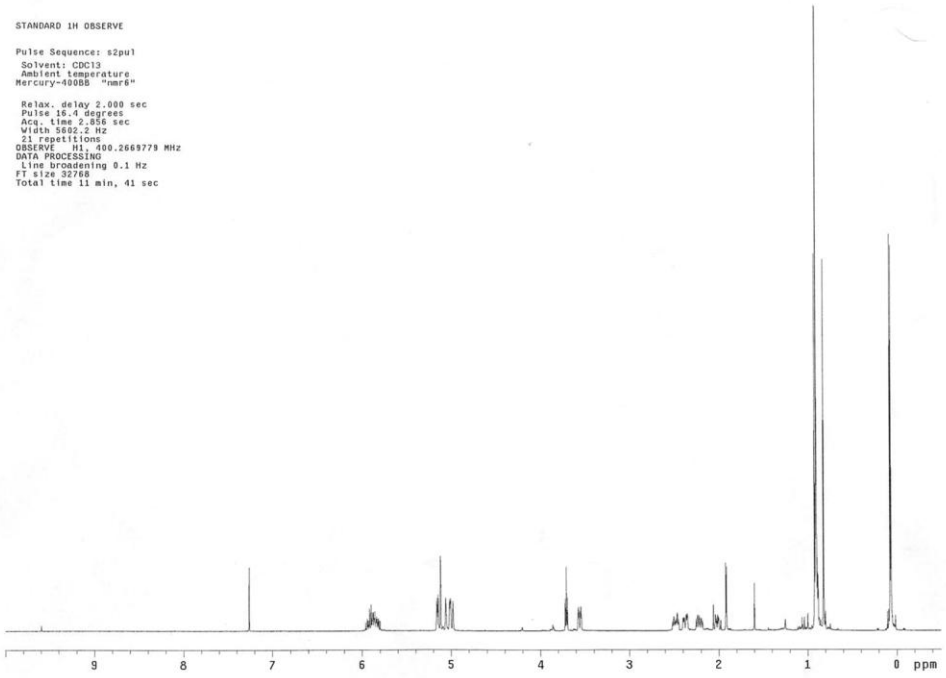


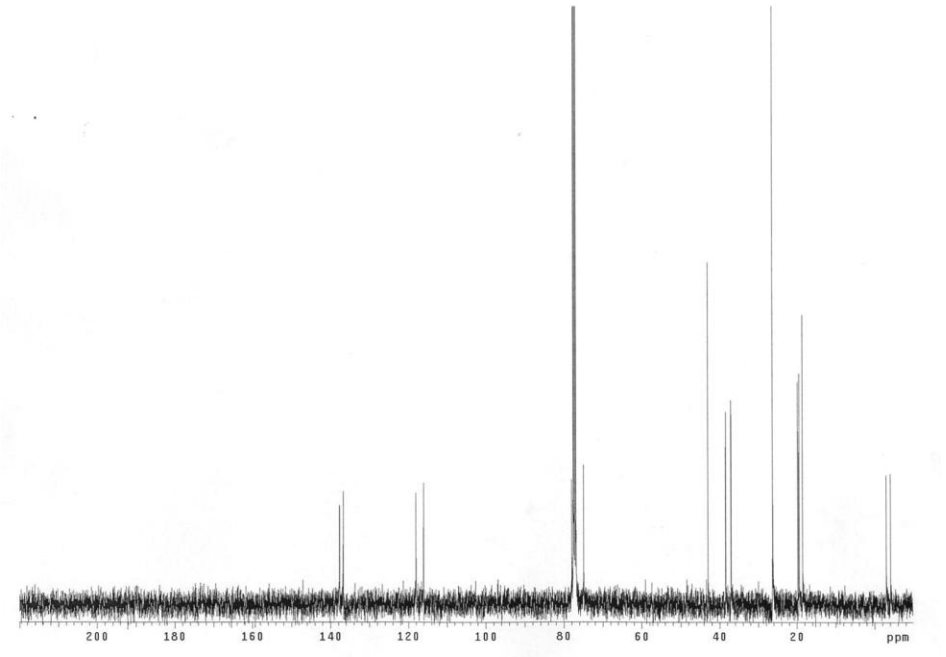




(4*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-5,5-dimethylnona-l,8-dien-4-ol ((*S*,*R*)-3.15)

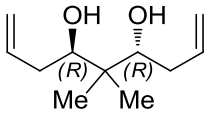


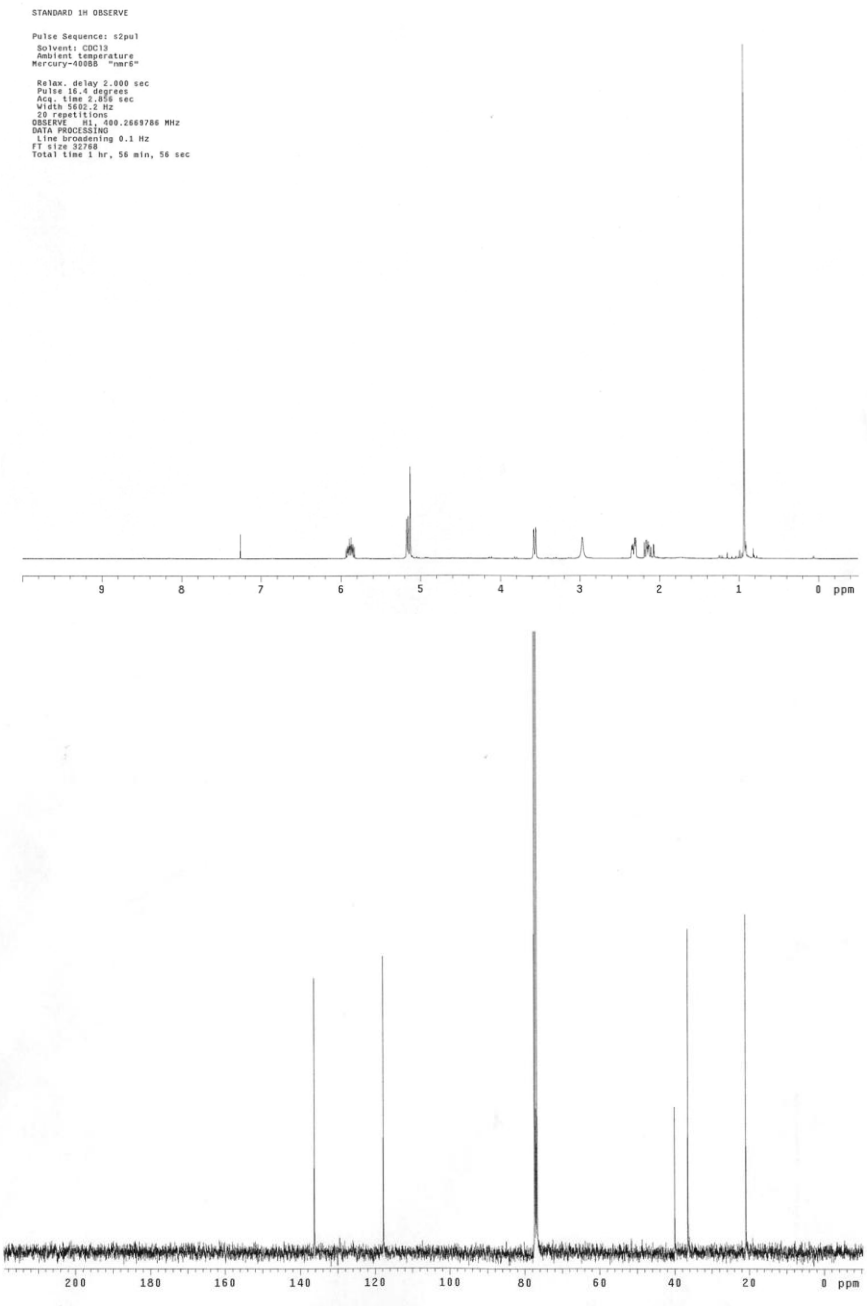




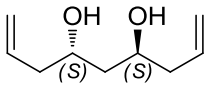
II Part Two: Elongation *via* Bis-allylation Reaction

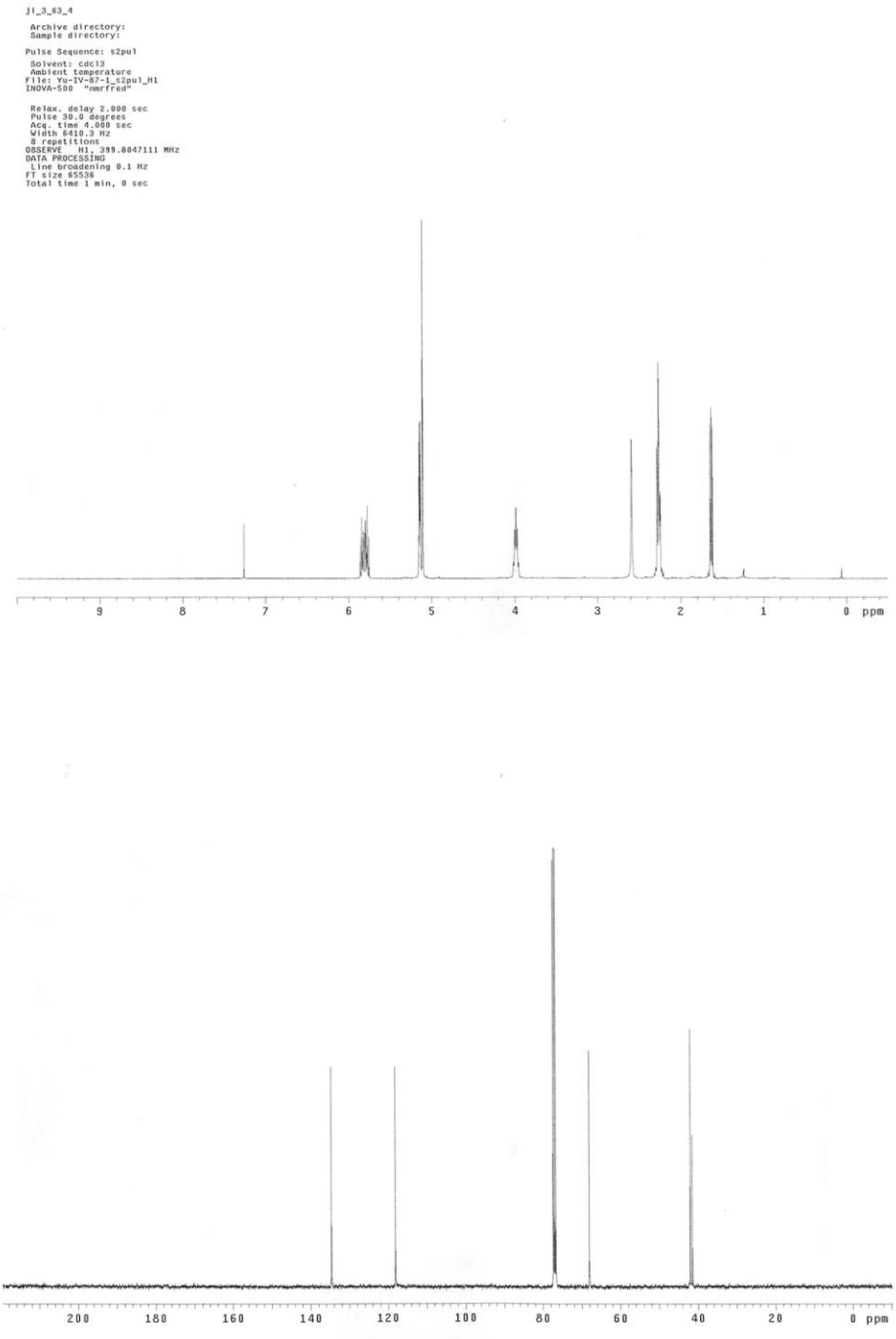
(4*R*,6*R*)-5,5-Dimethylnona-l,8-diene-4,6-diol ((*R*,*R*)-3.17)



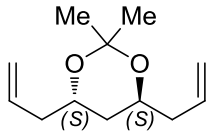


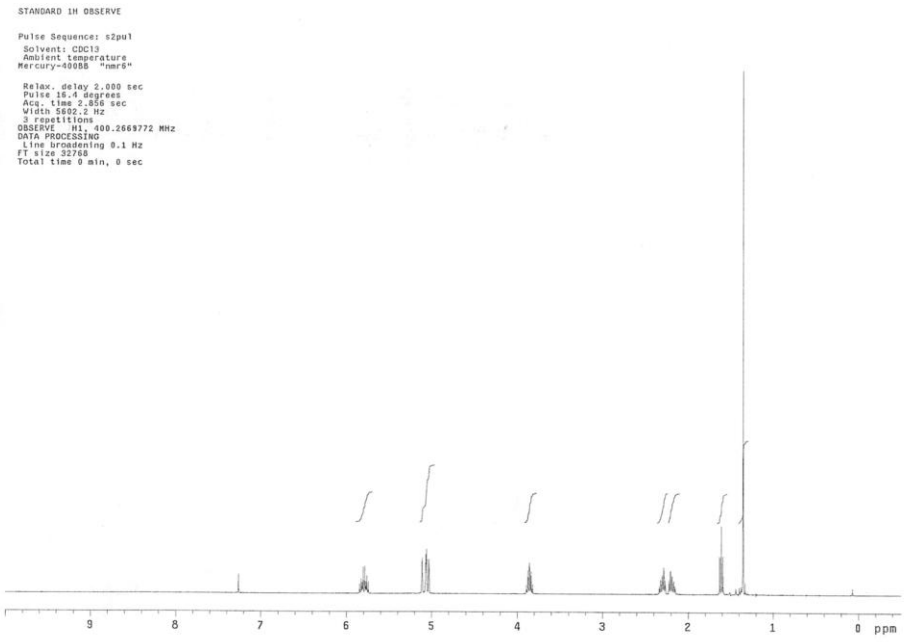
(4*S*,6*S*)-Nona-l,8-diene-4,6-diol ((*S*,*S*)-3.17)

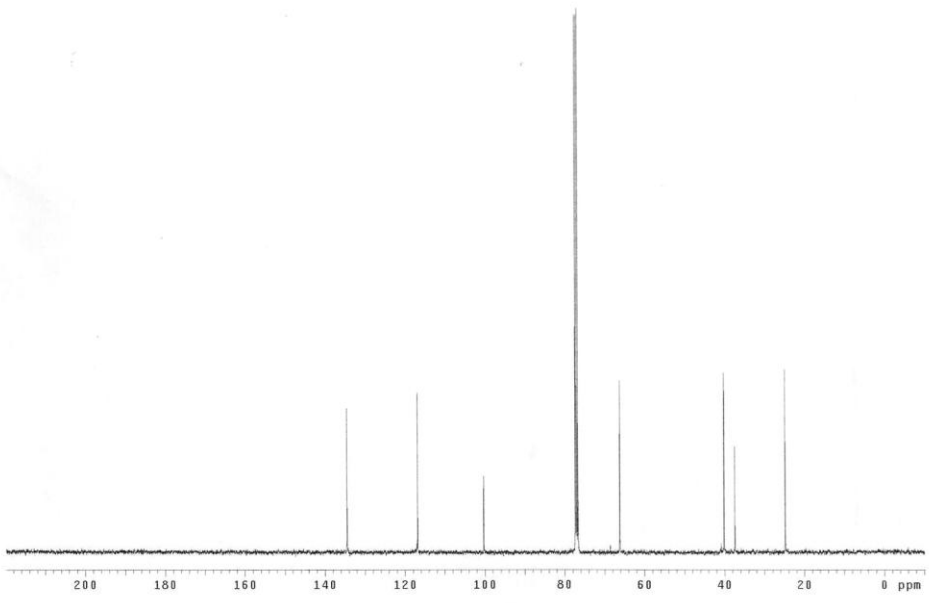




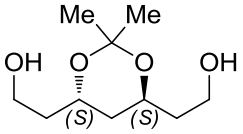
(4*S*,6*S*)-4,6-Diallyl-2,2-dimethyl-l,3-dioxane ((*S*,*S*)-3.24a)

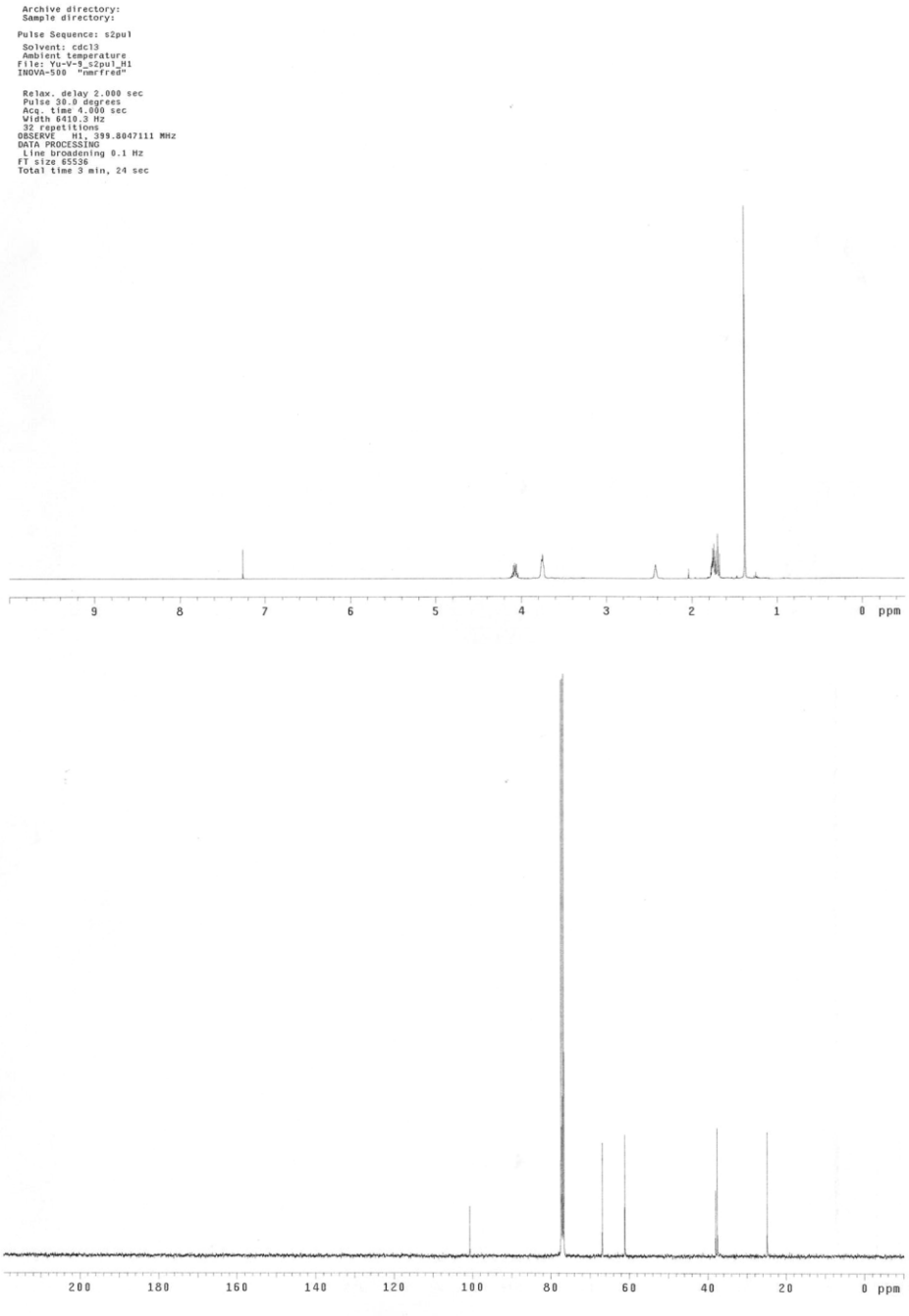




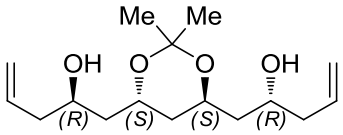


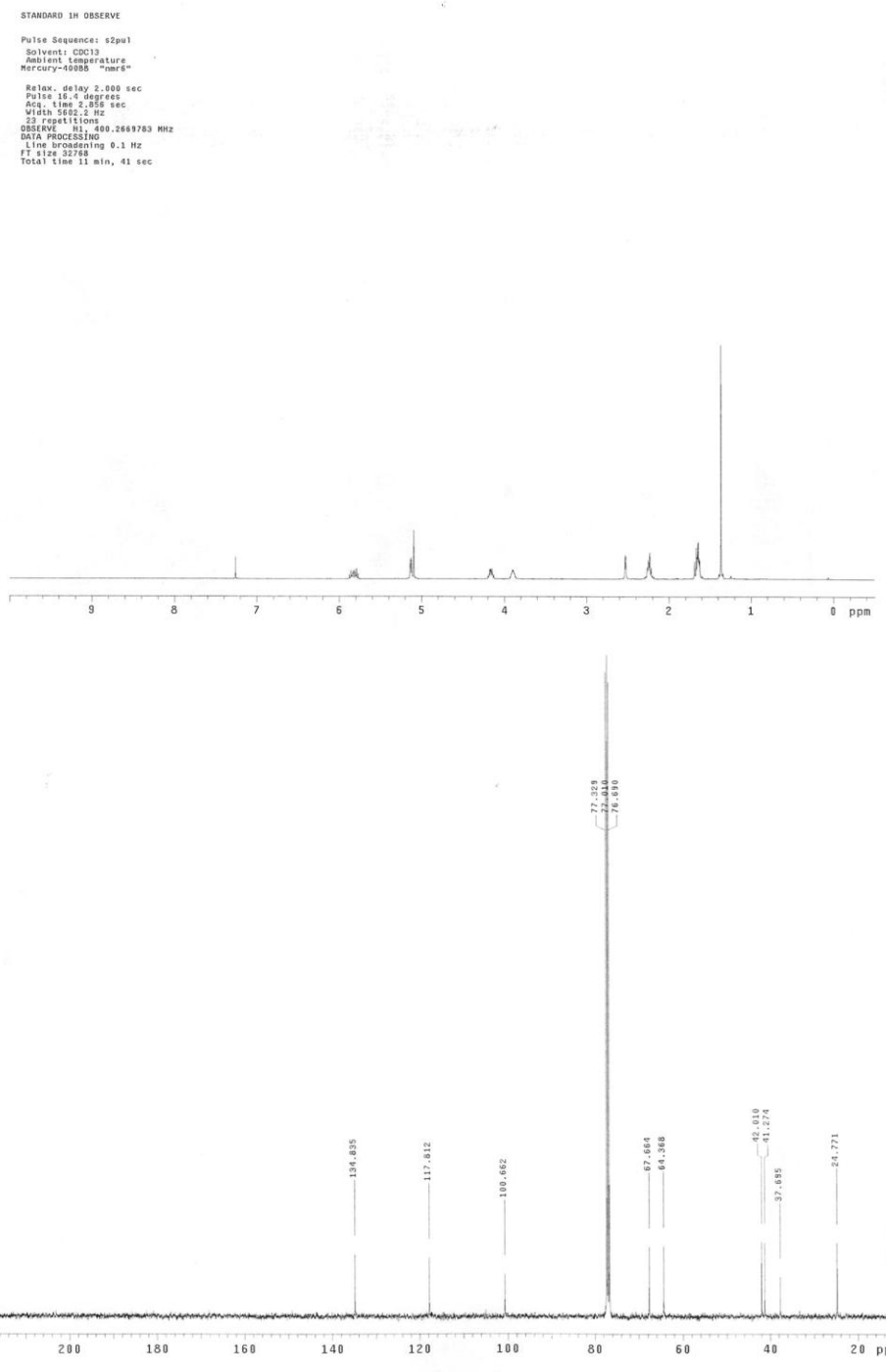
(3*S*,5*S*)-*O*-Isopropylidene-l,7-heptadiol ((*S*,*S*)-3.24)



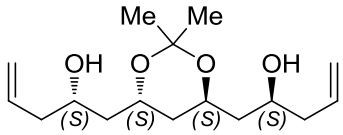


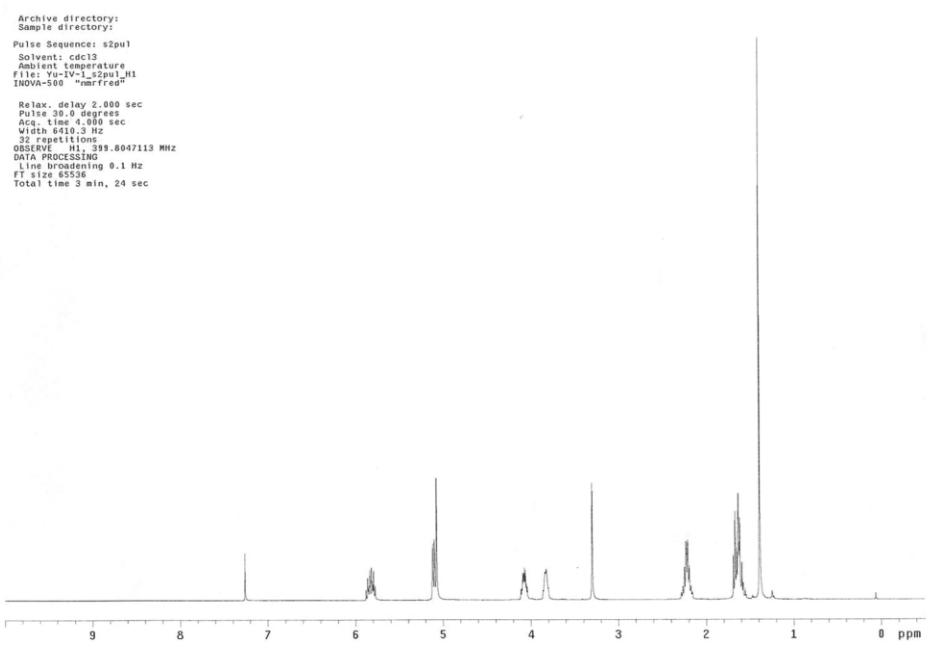
(2*R*,2'*R*)-1,1'-((4*S*,6*S*)-2,2-Dimethyl-l,3-dioxane-4,6-diyl)dipent-4-en-2-ol ((*R*,*S*,*S*,*R*)-3.25)

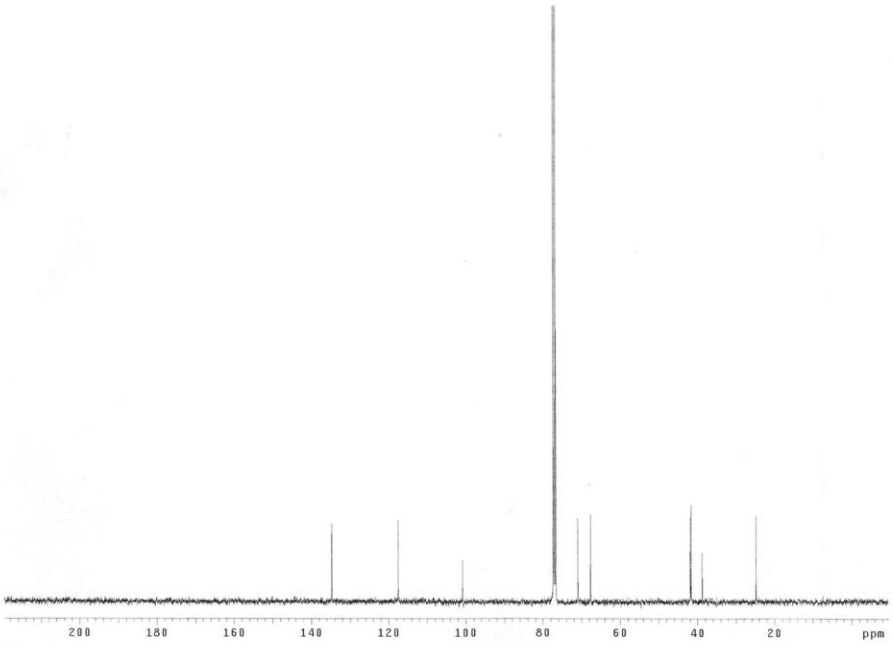




(2*S*,2'*S*)-l,l'-((4*S*,6*S*)-2,2-Dimethyl-l,3-dioxane-4,6-diyl)dipent-4-en-2-ol ((*S*,*S*,*S*,*S*)-3.25)



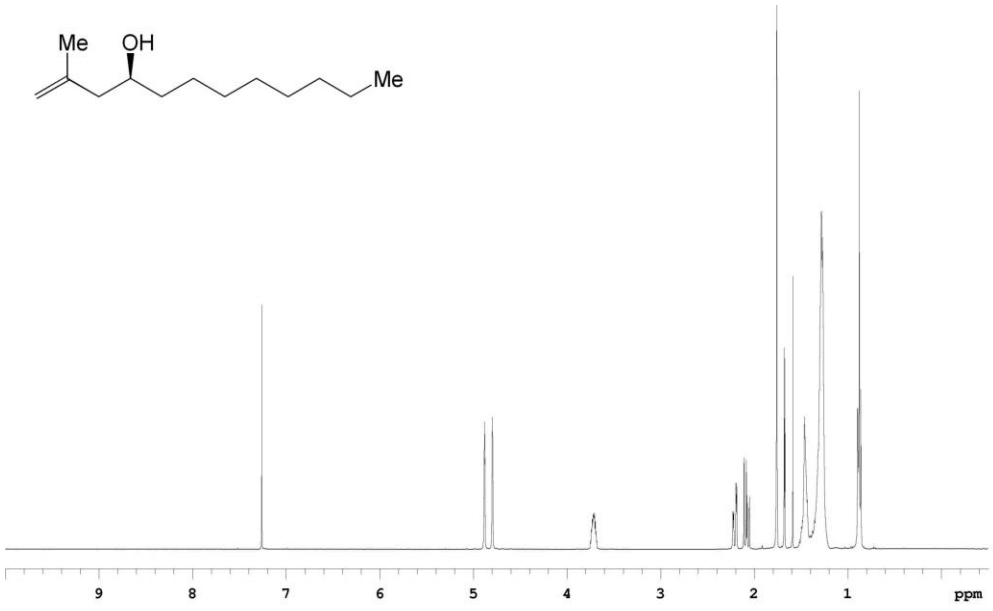


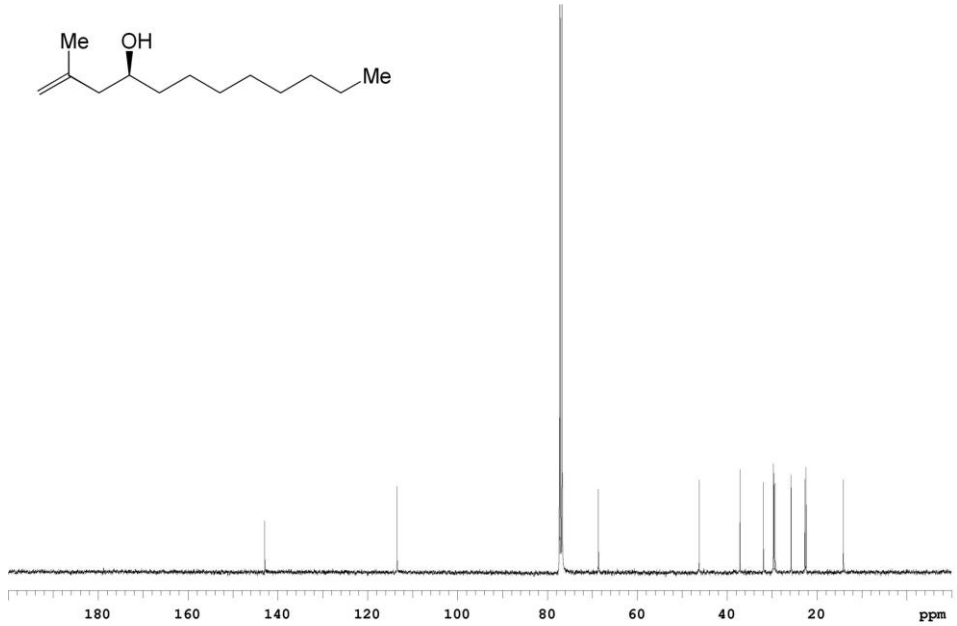


Chapter 3

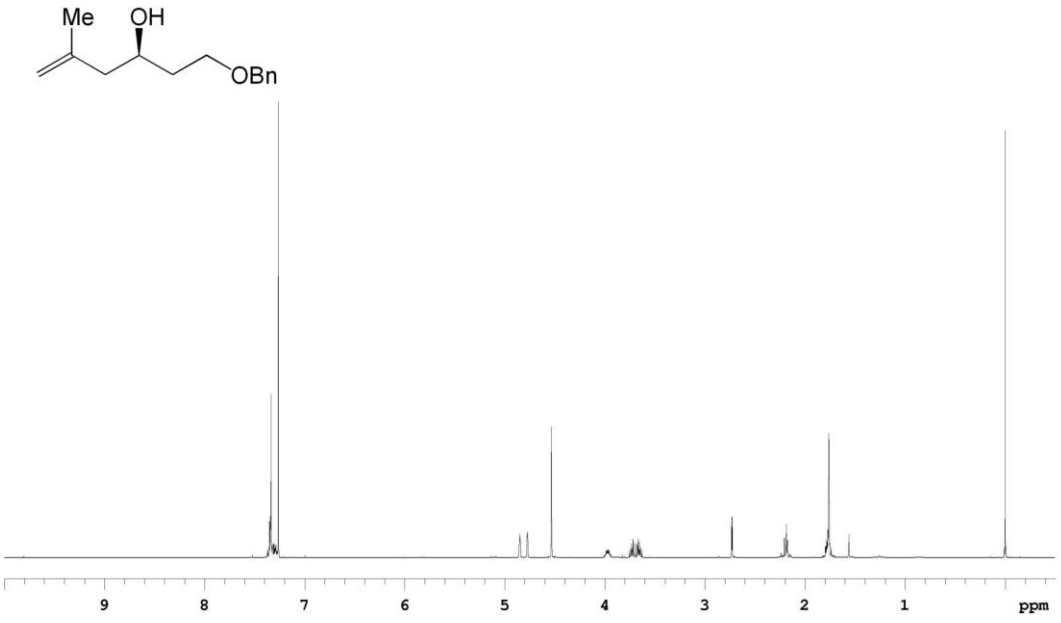
I Part One: Spectra data of Methallylation Products

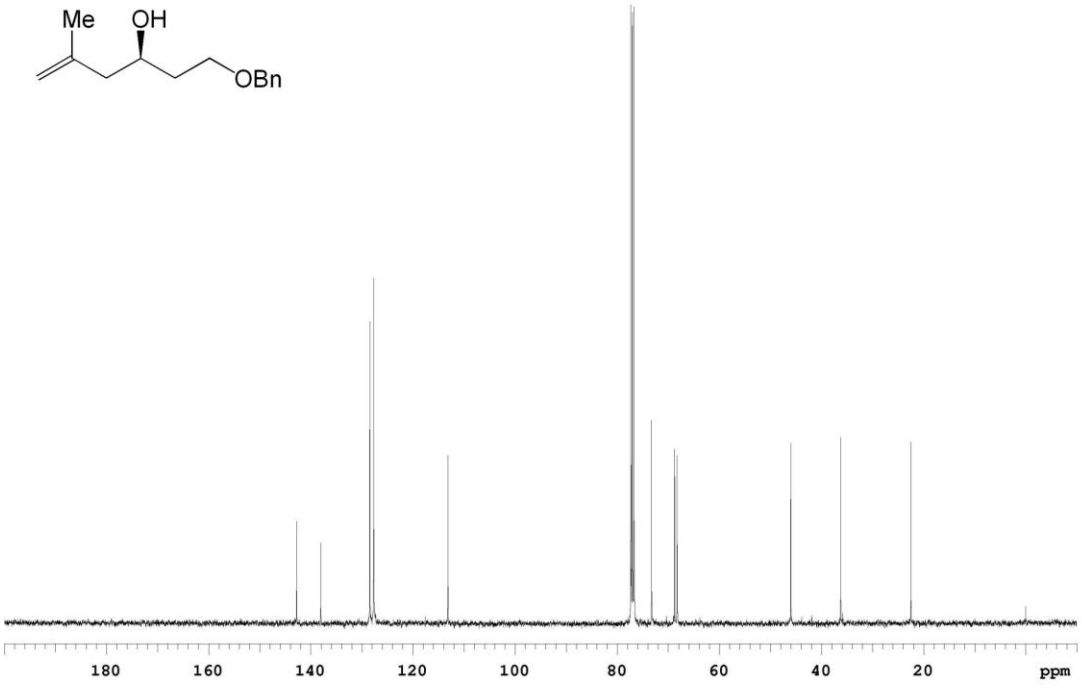
(S)-2-methyldodec-1-en-4-ol (4.29)



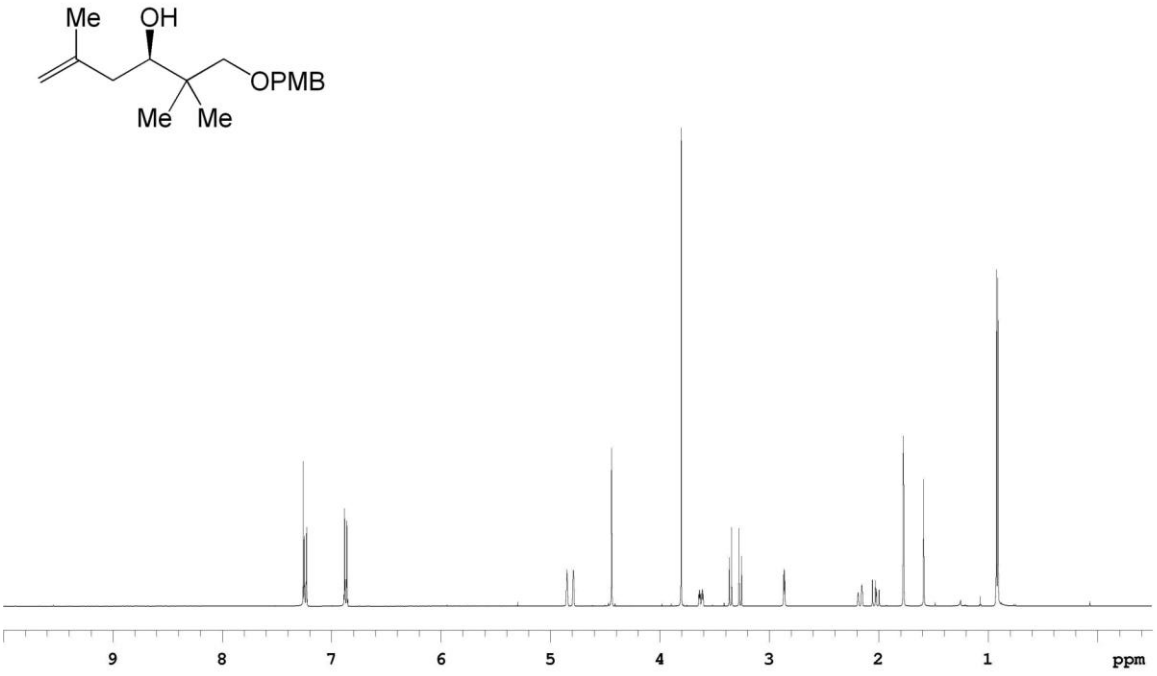


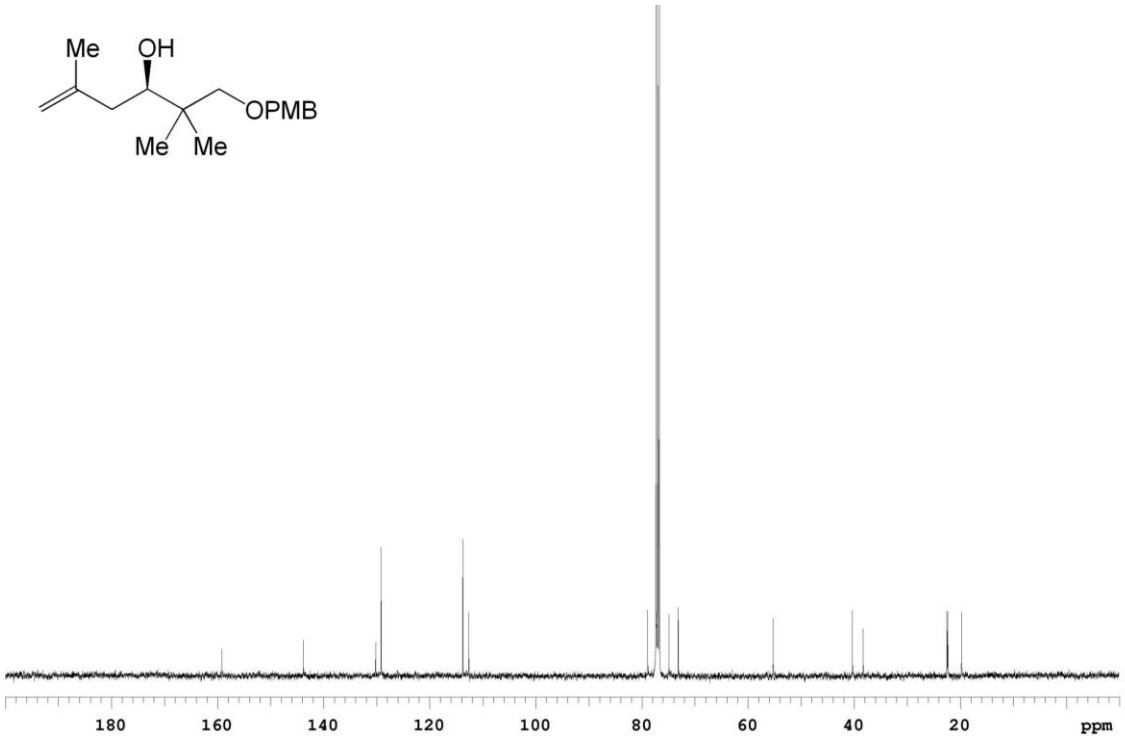
(R)-1-(benzyloxy)-5-methylhex-5-en-3-ol (4.32)



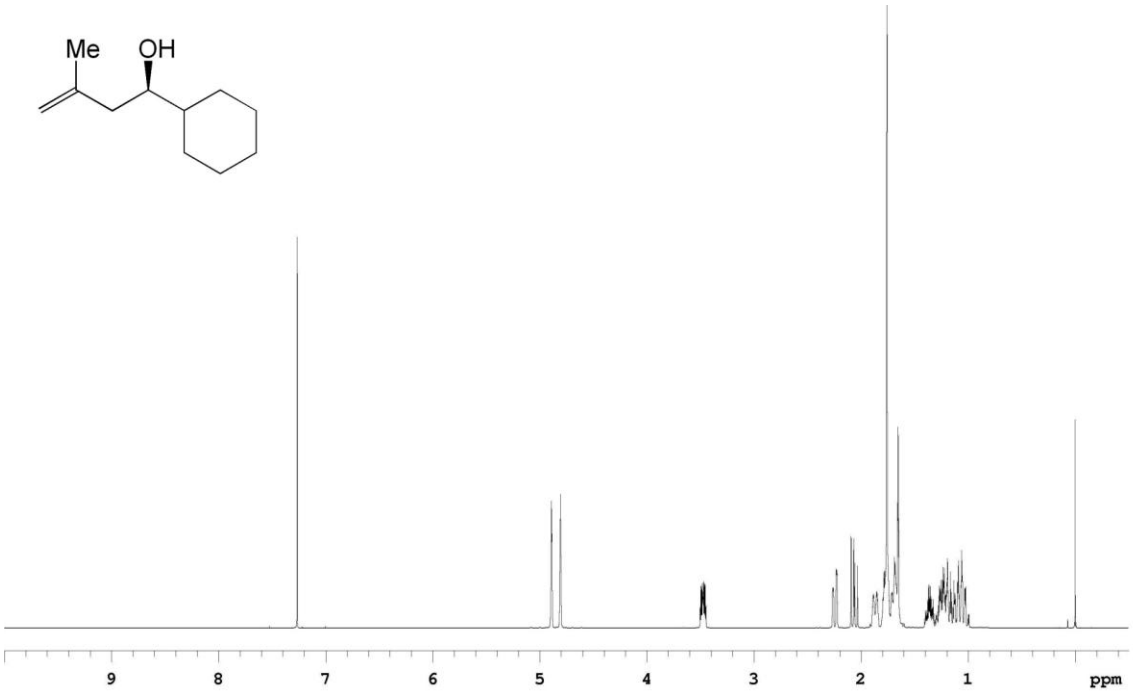


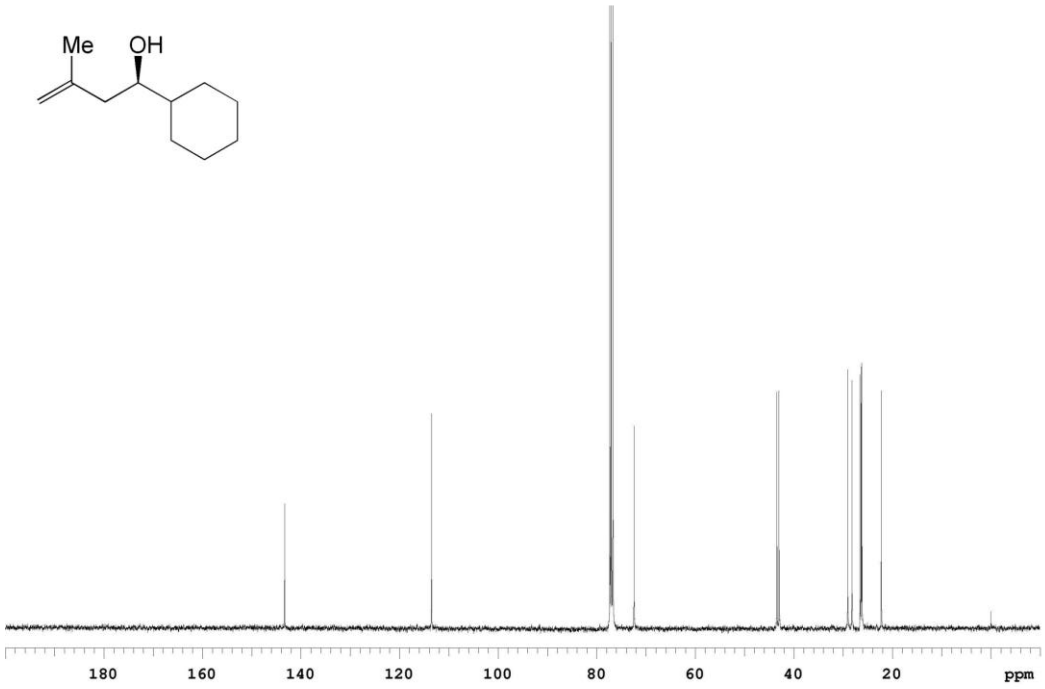
(R)-1-(4-methoxybenzyloxy)-2,2,5-trimethylhex-5-en-3-ol (4.35)



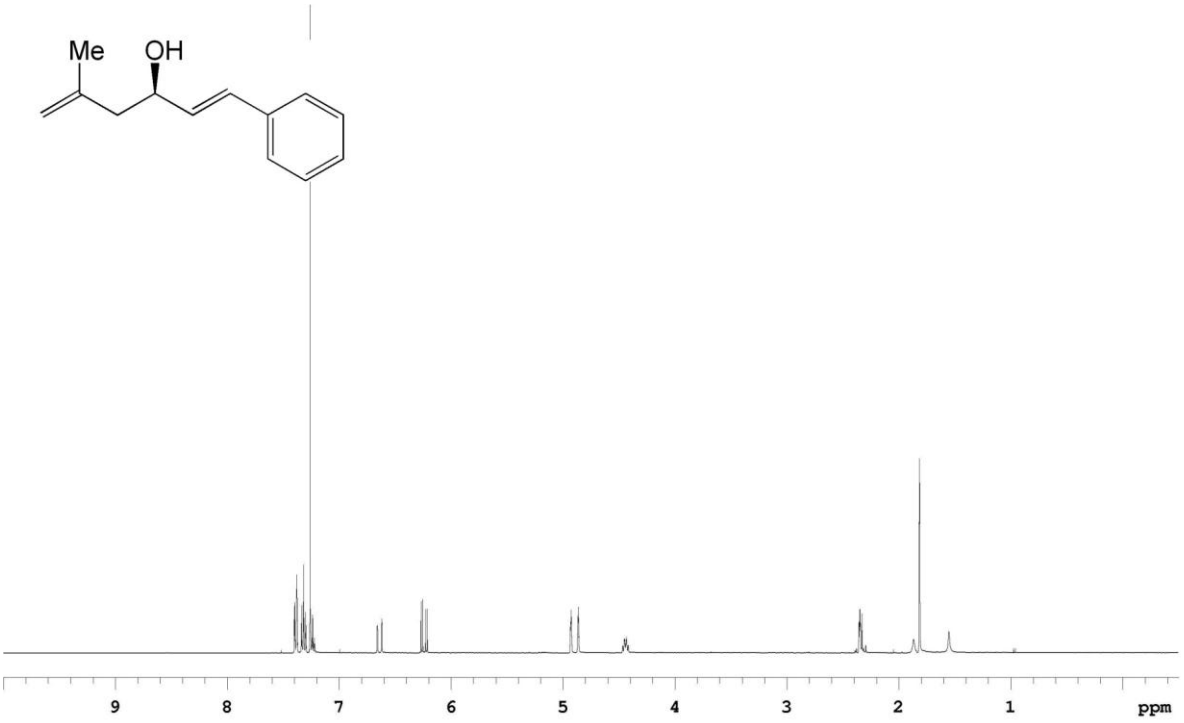


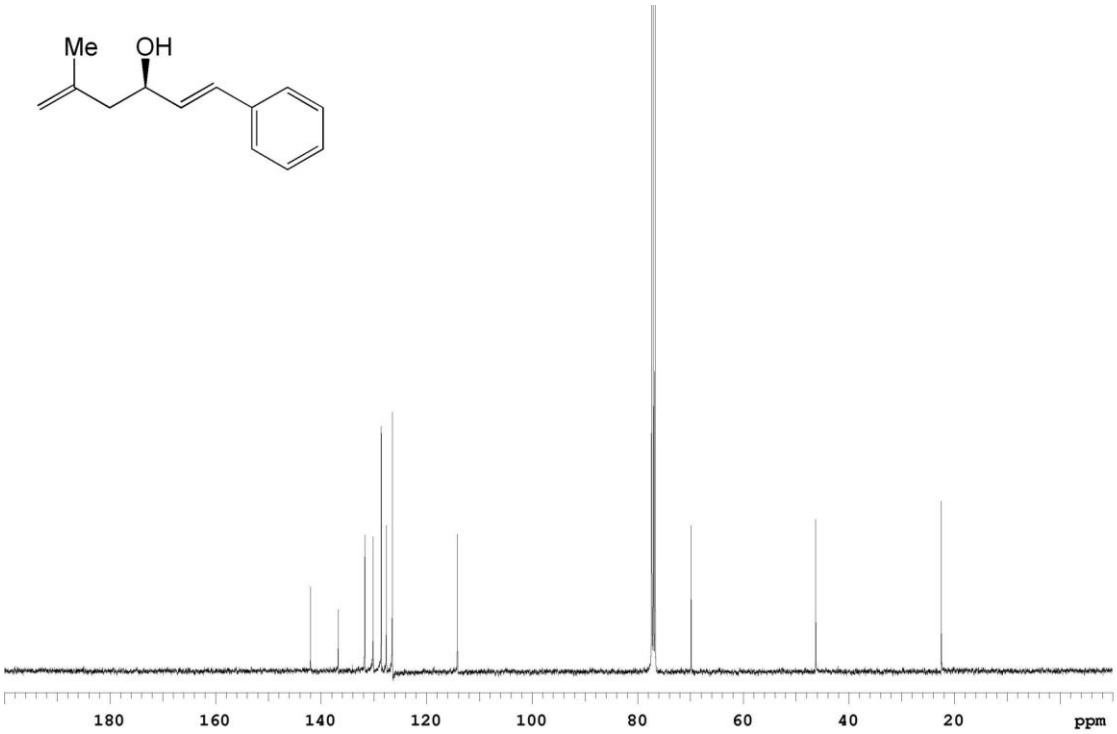
(R)-1-cyclohexyl-3-methylbut-3-en-1-ol (4.30)



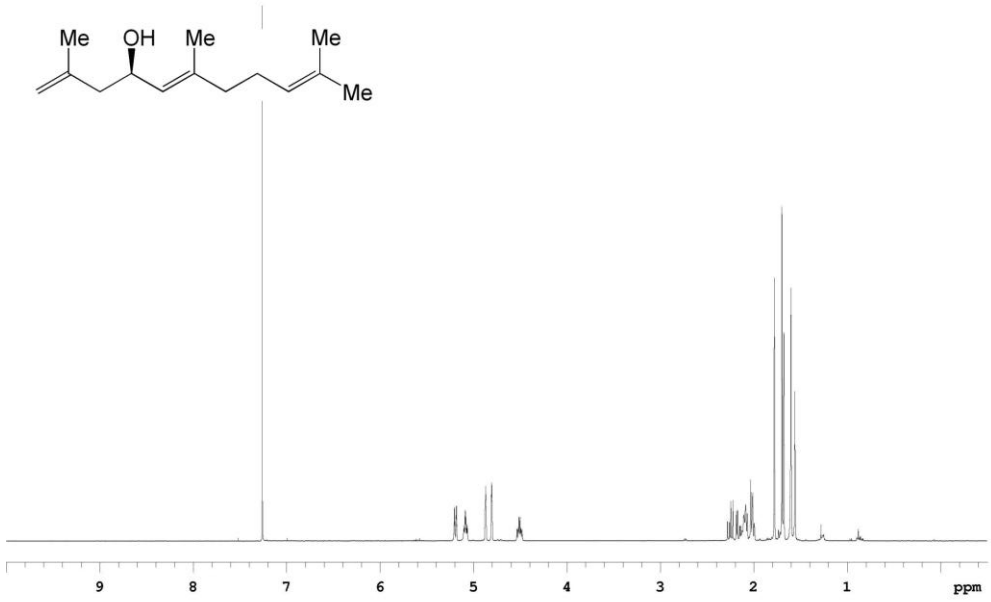


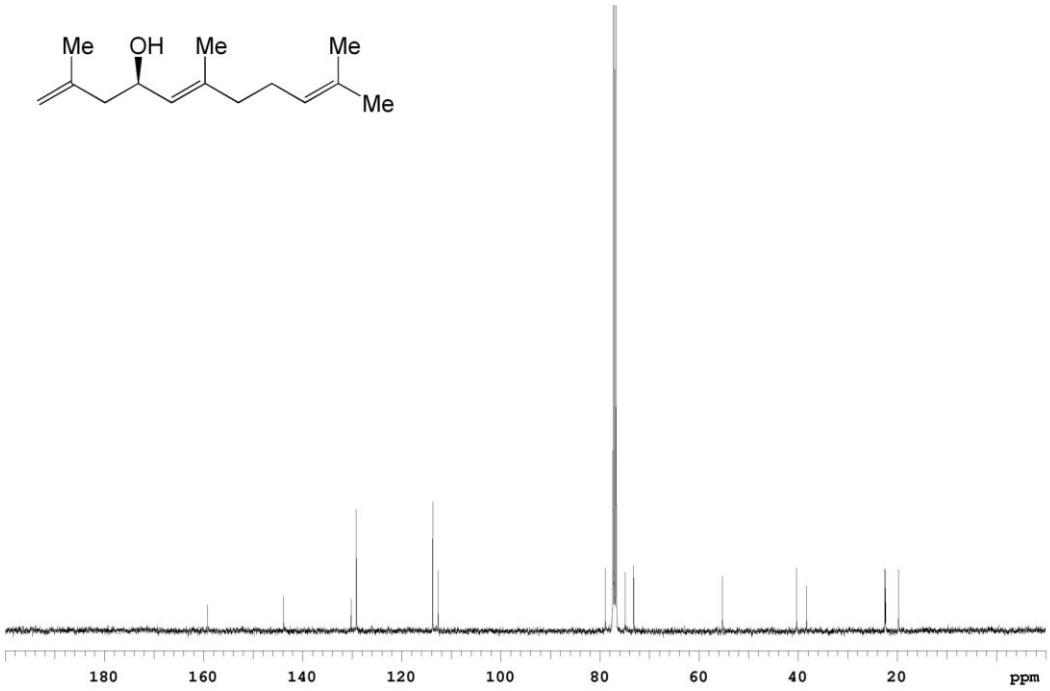
(R,E)-5-methyl-1-phenylhexa-1,5-dien-3-ol (4.33)



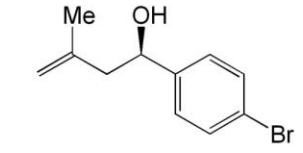


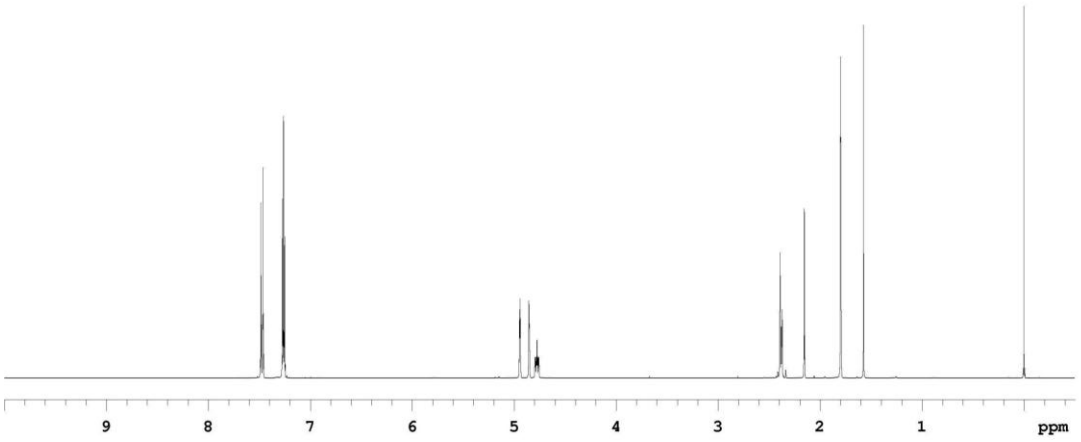
(R,E)-2,6,10-trimethylundeca-1,5,9-trien-4-ol (4.36)

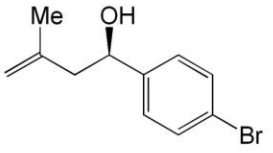




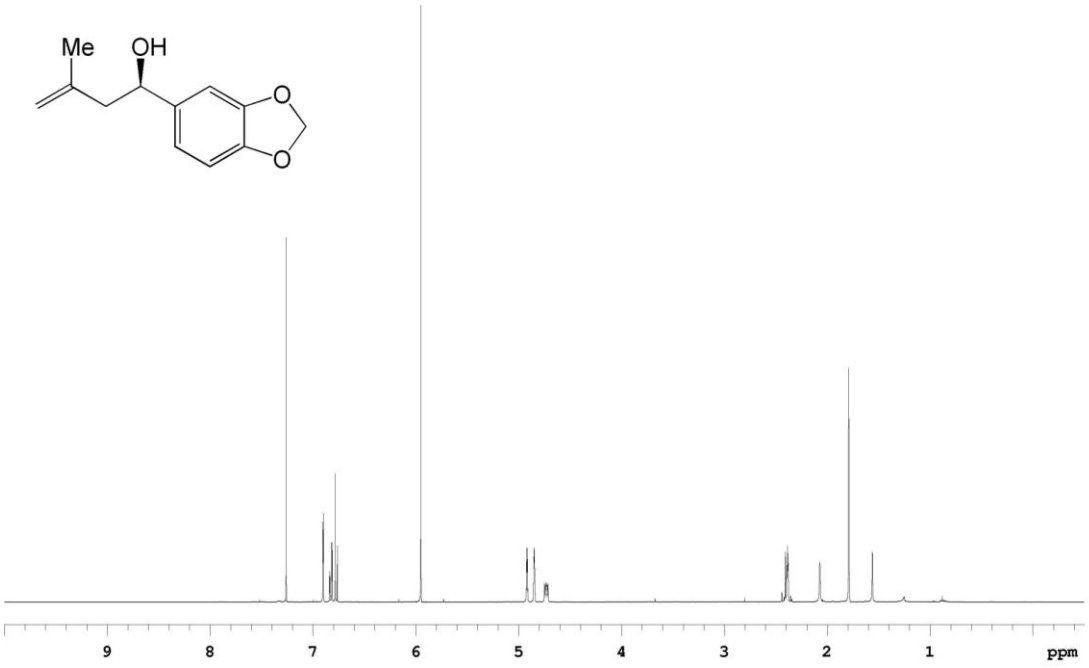
(R)-1-(4-bromophenyl)-3-methylbut-3-en-1-ol (4.34)

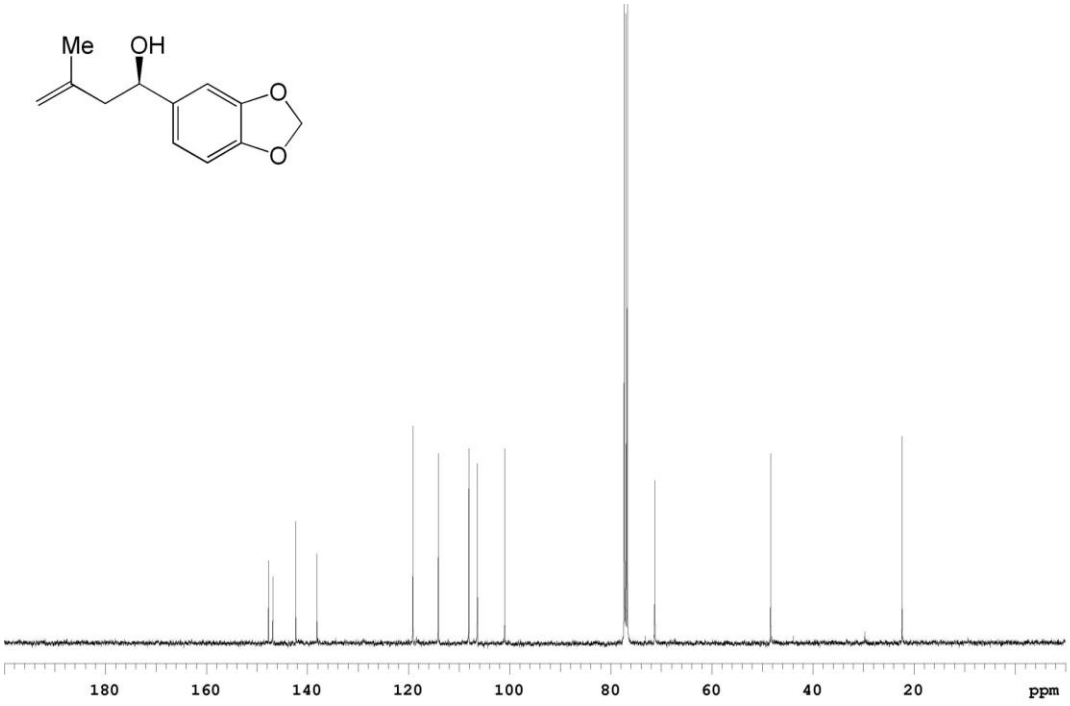




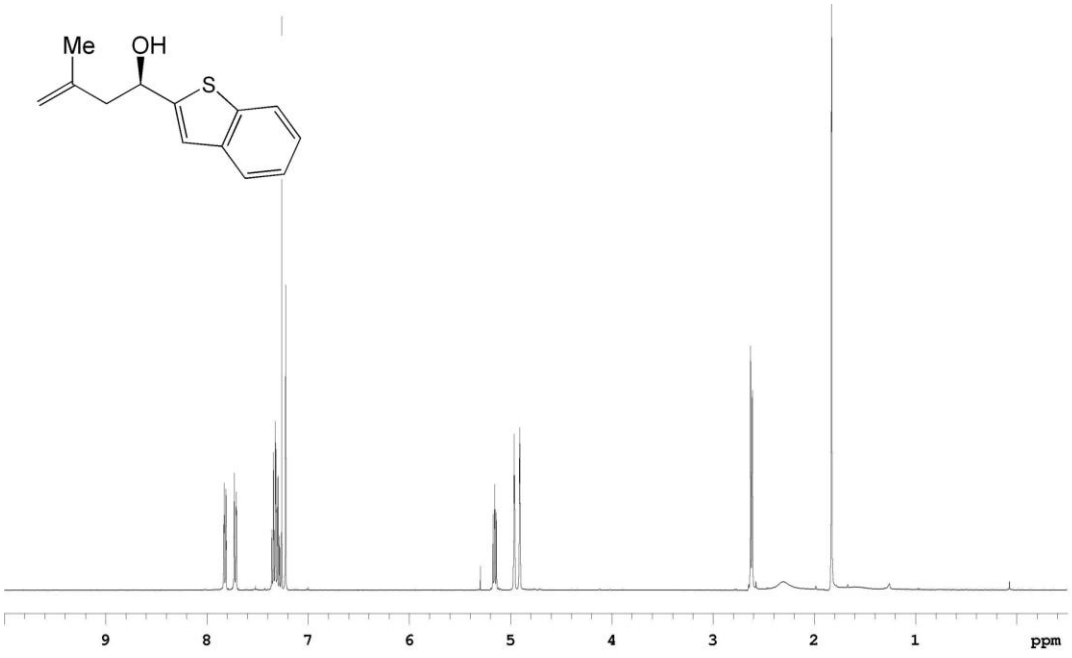


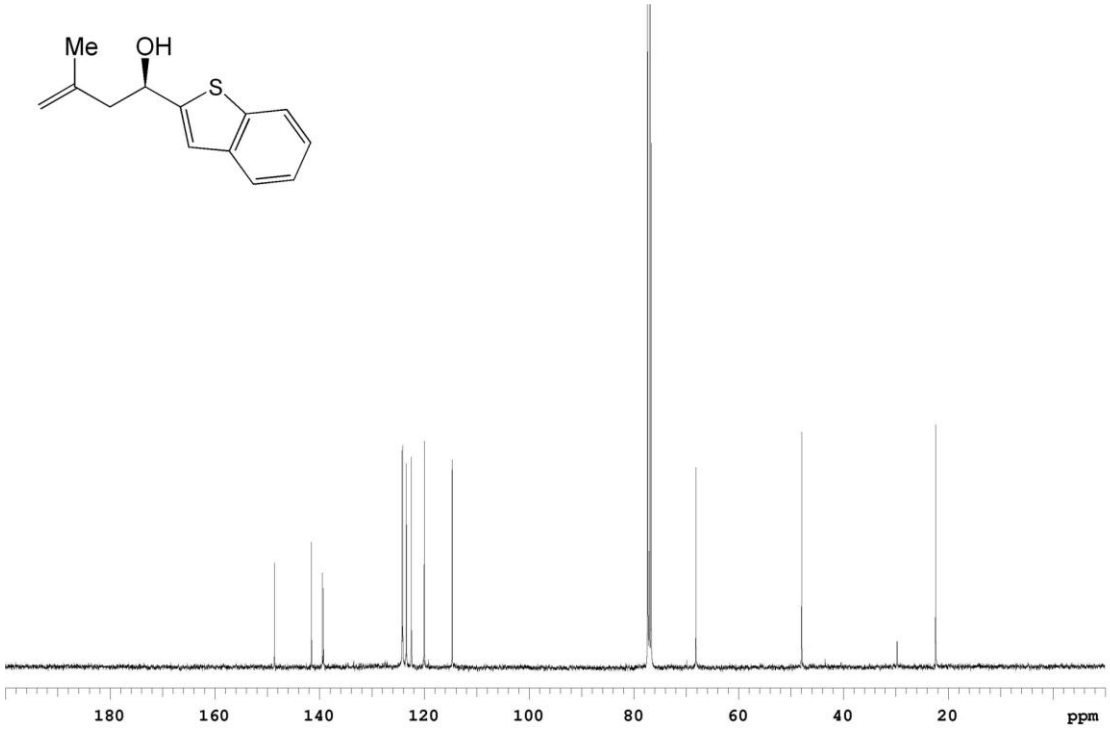
(R)-1-(benzo[d][1,3]dioxol-5-yl)-3-methylbut-3-en-1-ol (4.31)





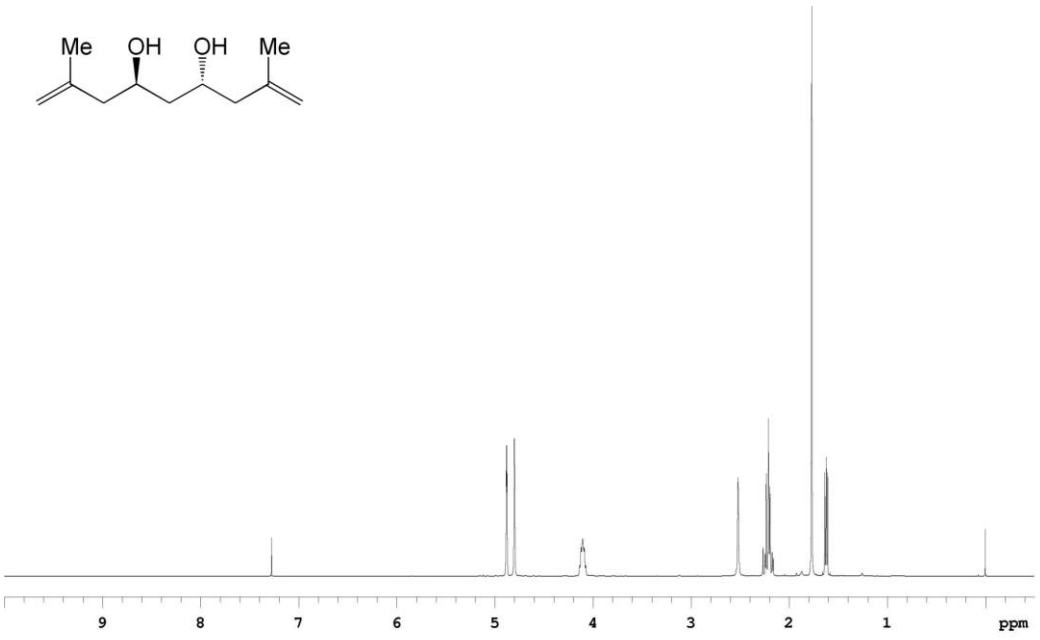
(R)-1-(benzo[b]thiophen-2-yl)-3-methylbut-3-en-1-ol (4.37)

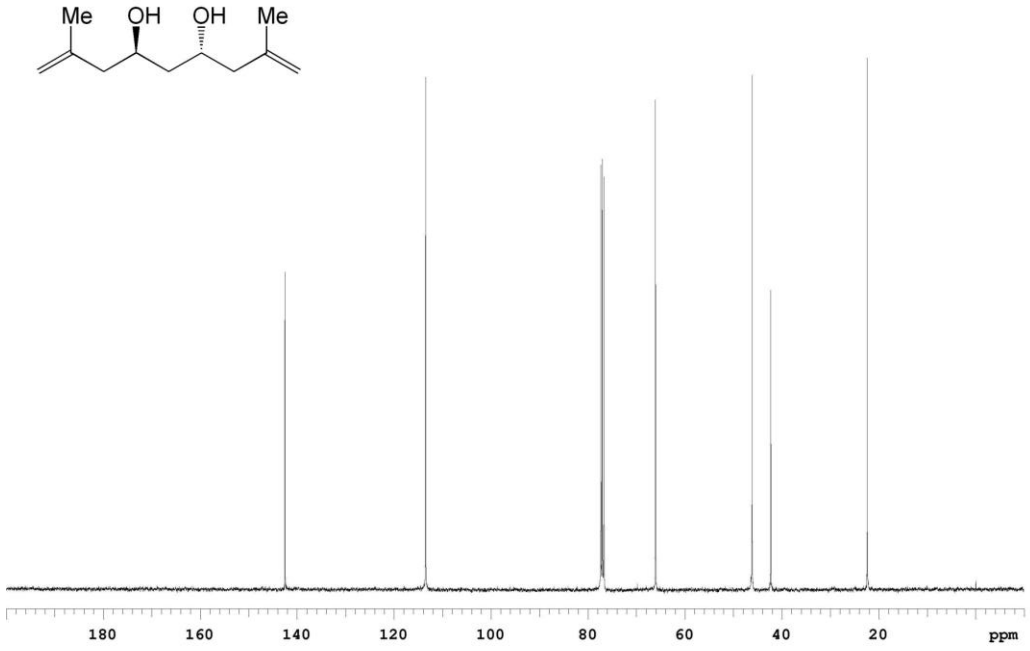




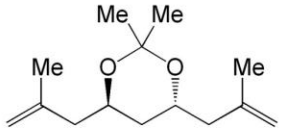
I.I Experiment details of Bis-methallylation of Propanediol

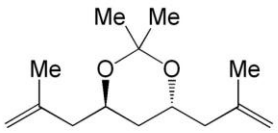
(4R,6R)-2,8-dimethylnona-1,8-diene-4,6-diol (4.39)



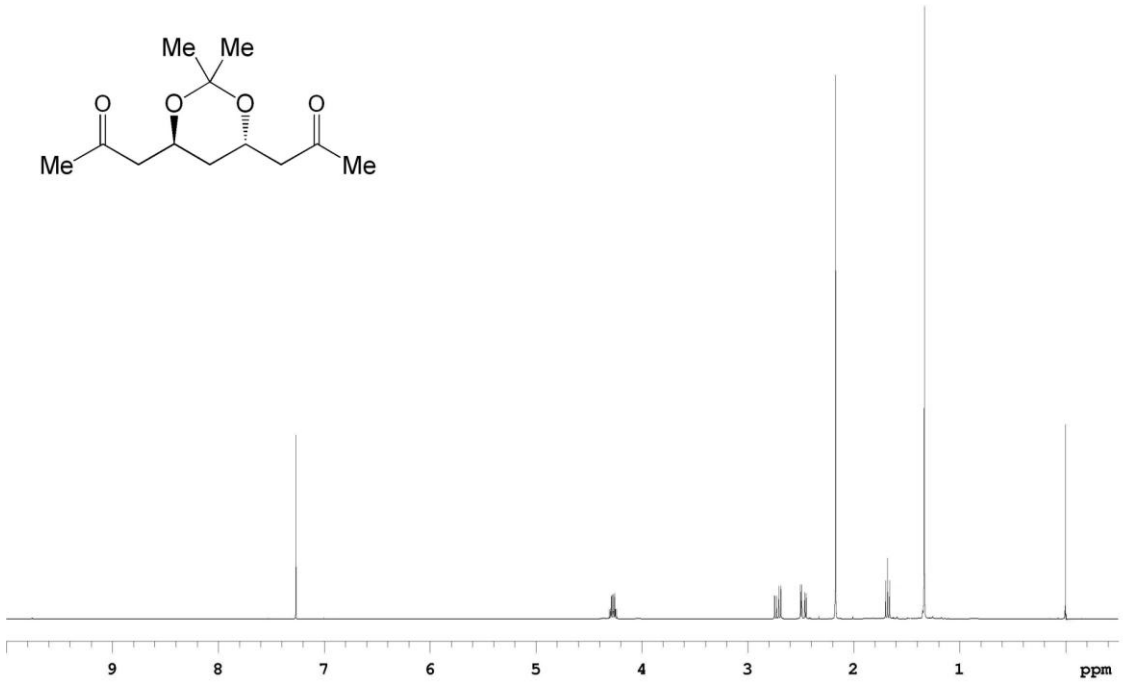


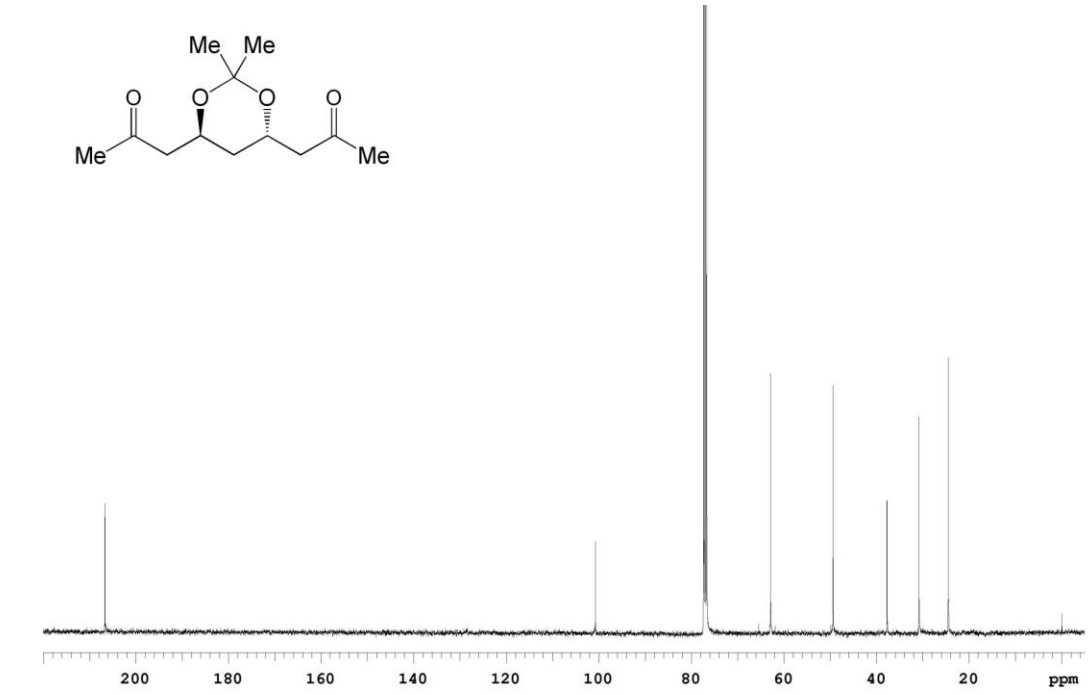
(4R,6R)-2,2-dimethyl-4,6-bis(2-methylallyl)-1,3-dioxane (4.40)





1,1'-((4S,6S)-2,2-dimethyl-1,3-dioxane-4,6-diyl)dipropan-2-one (4.41)

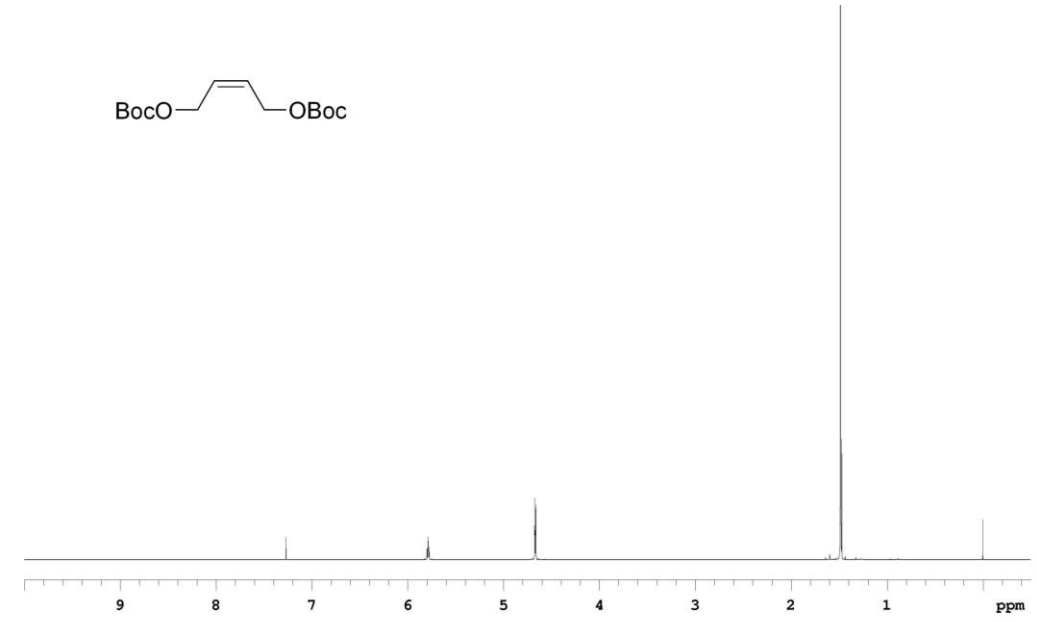


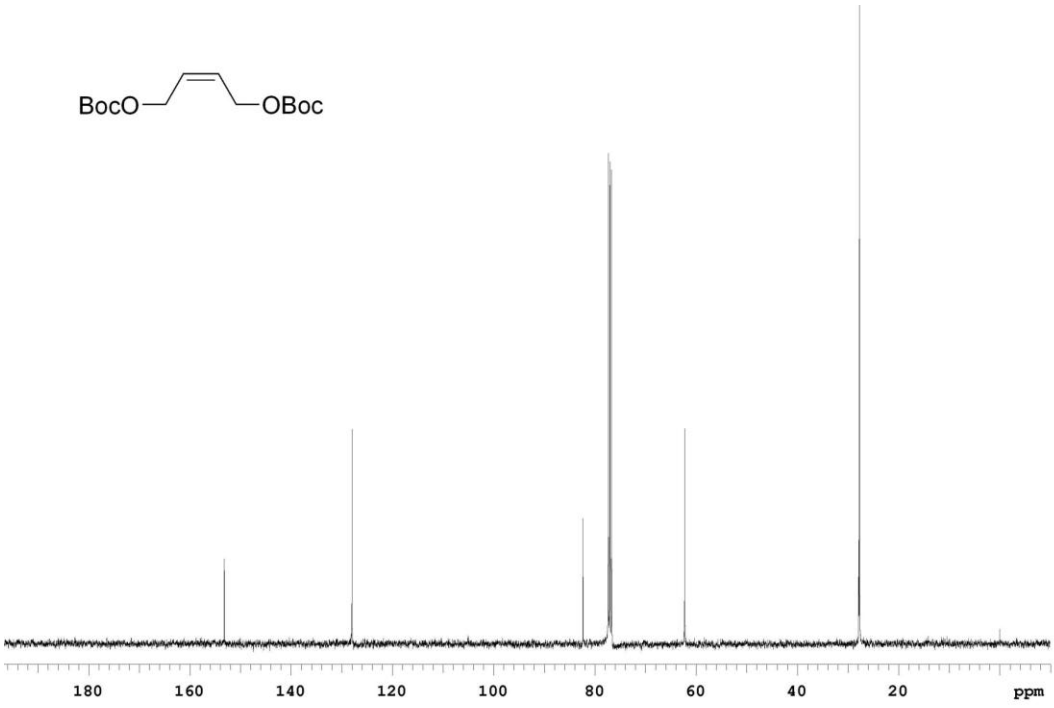


Chapter 4

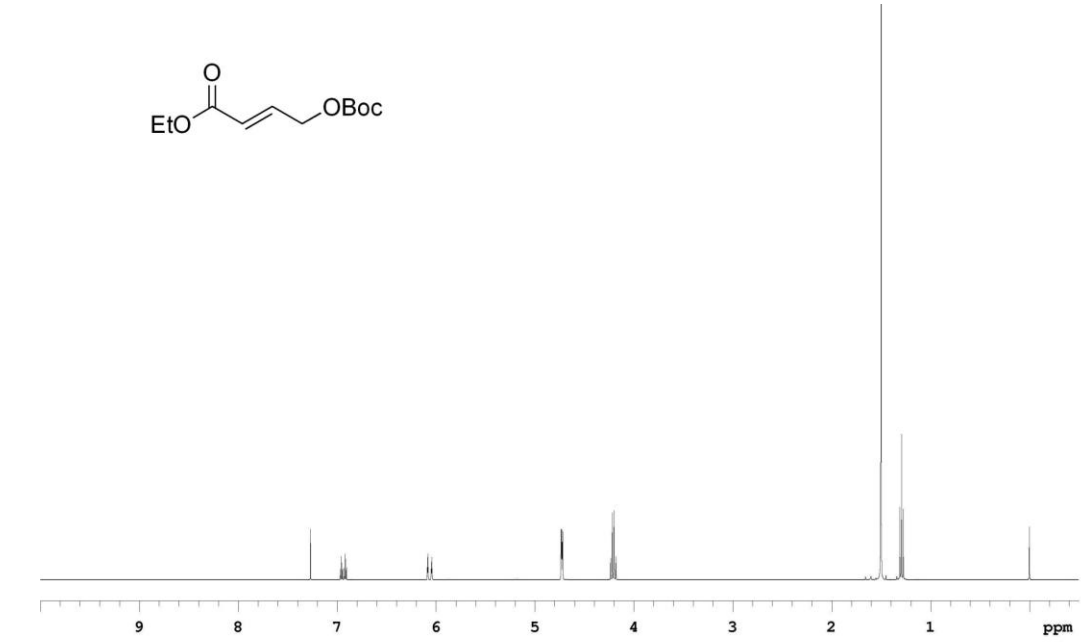
III Part Two: Spectra data of Vinylogous Aldol Products

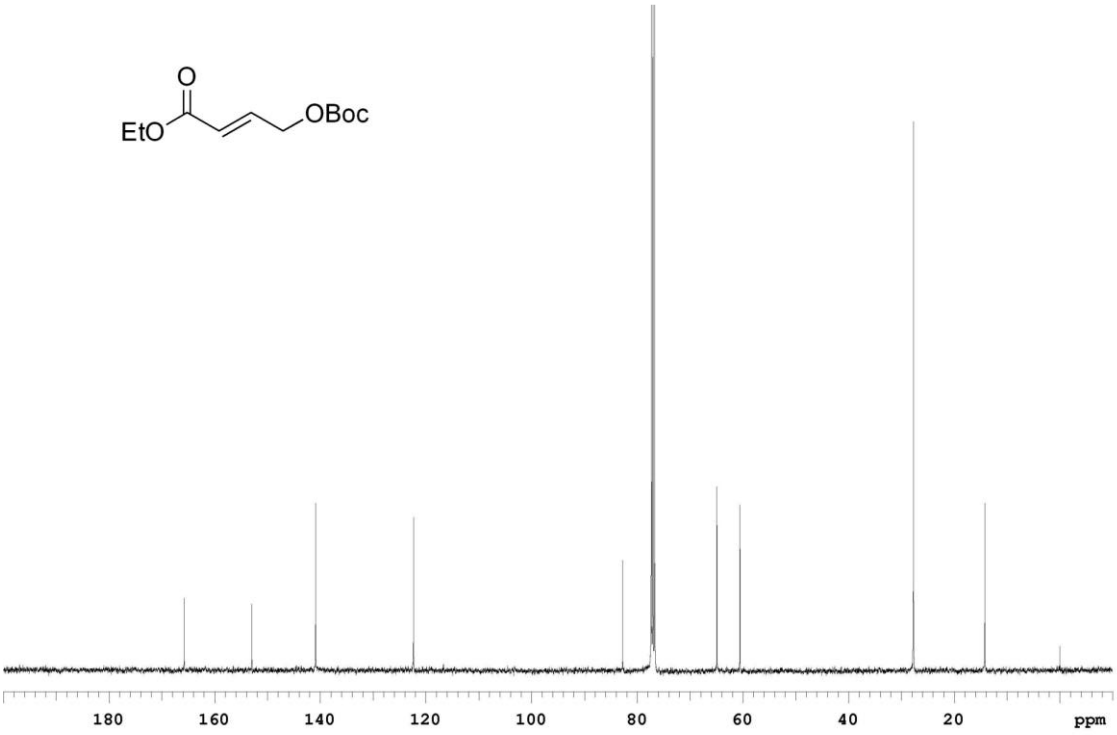
(*Z*)-but-2-ene-1,4-diyl tert-butyl dicarbonate



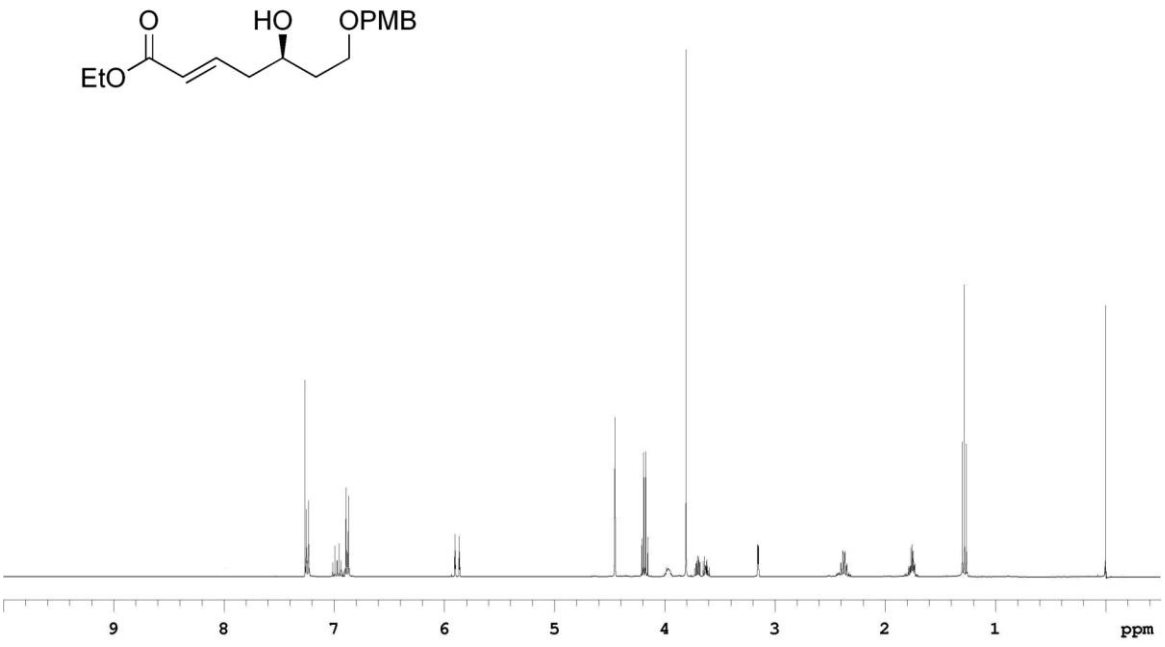


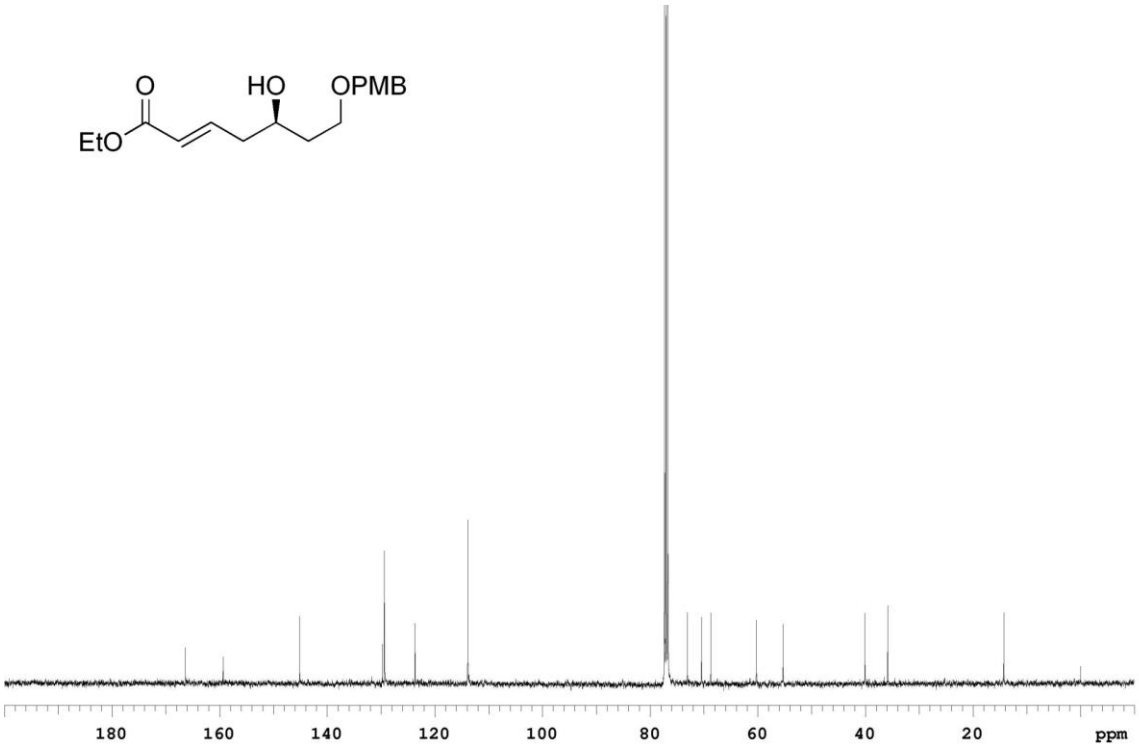
(*E*)-ethyl 4-(tert-butoxycarbonyloxy)but-2-enoate (4.48)



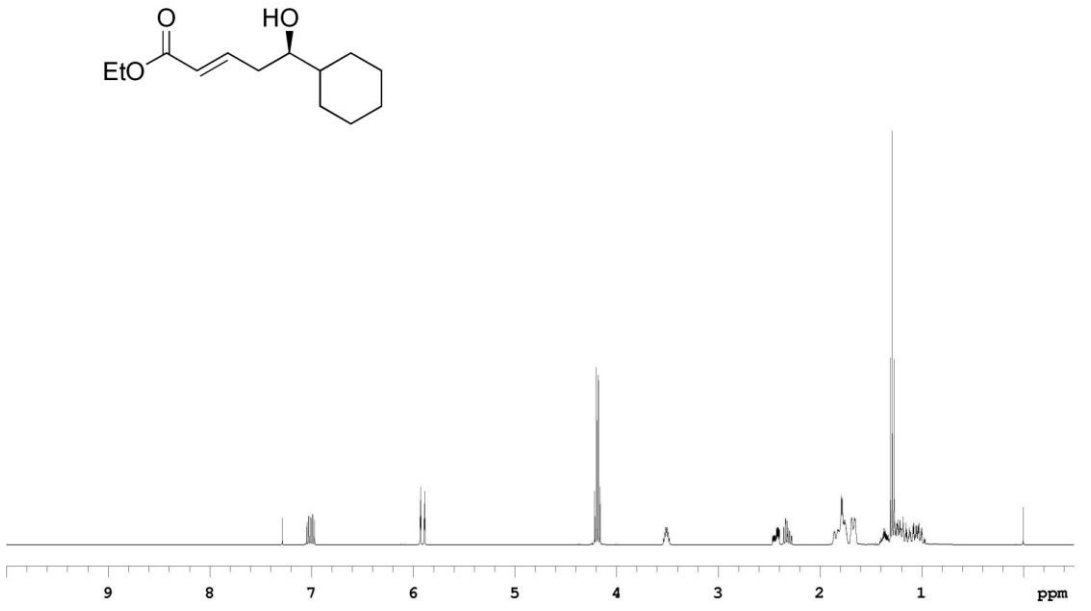


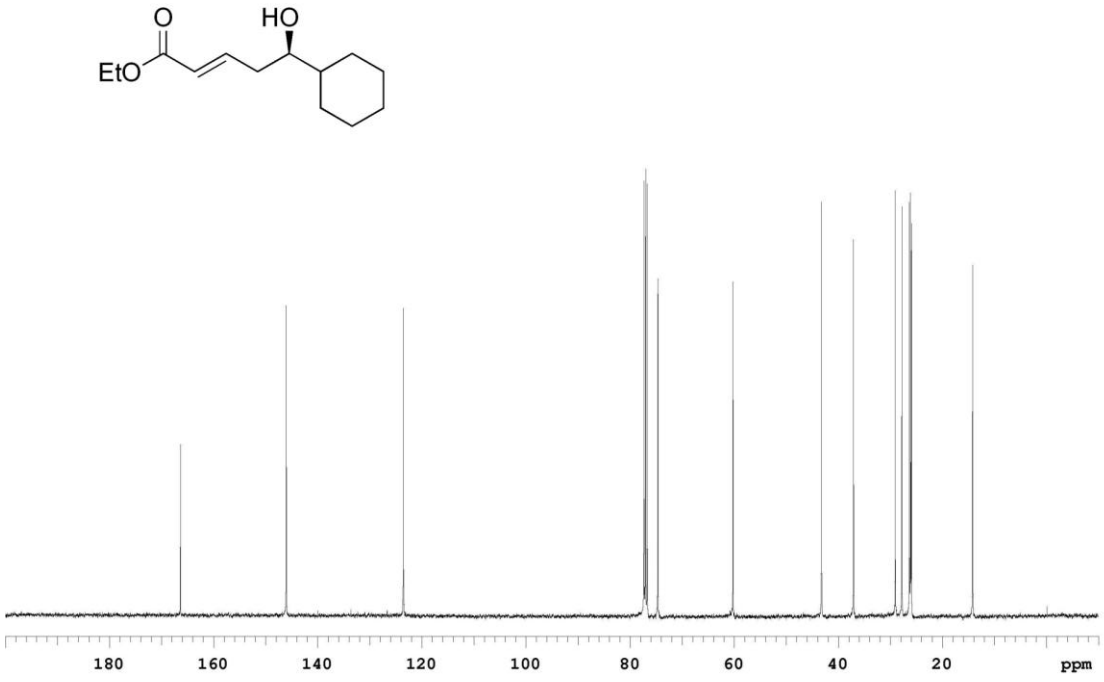
(*R*)-(*E*)-ethyl 5-hydroxy-7-(4-methoxybenzyloxy)hept-2-enoate (4.69)



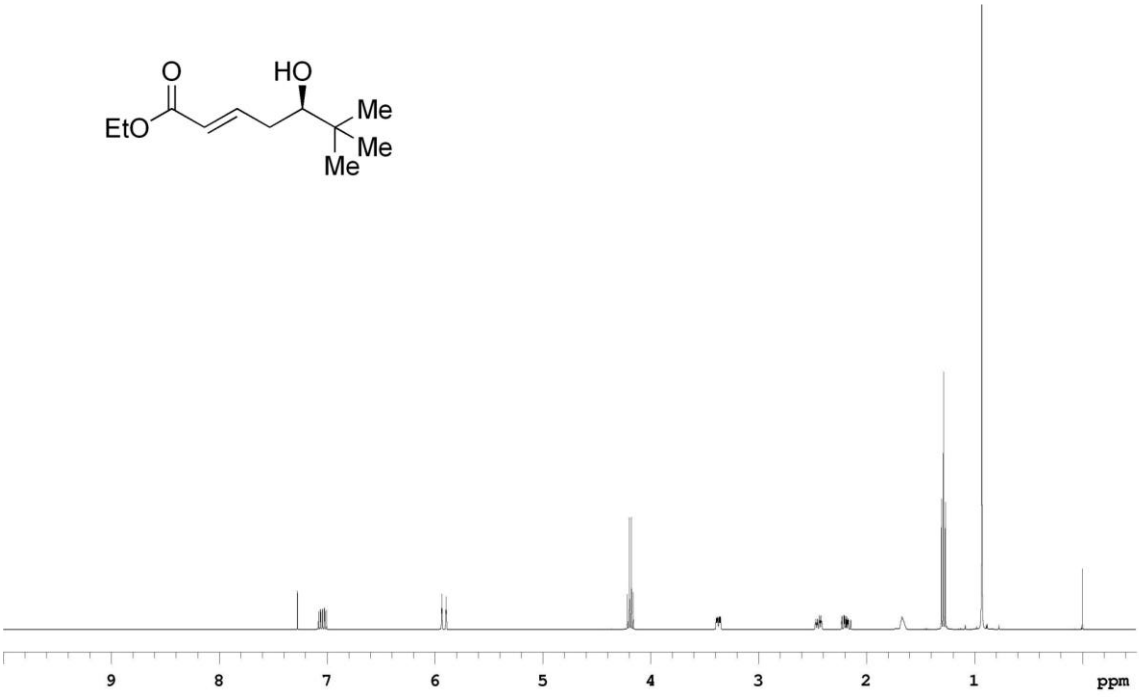


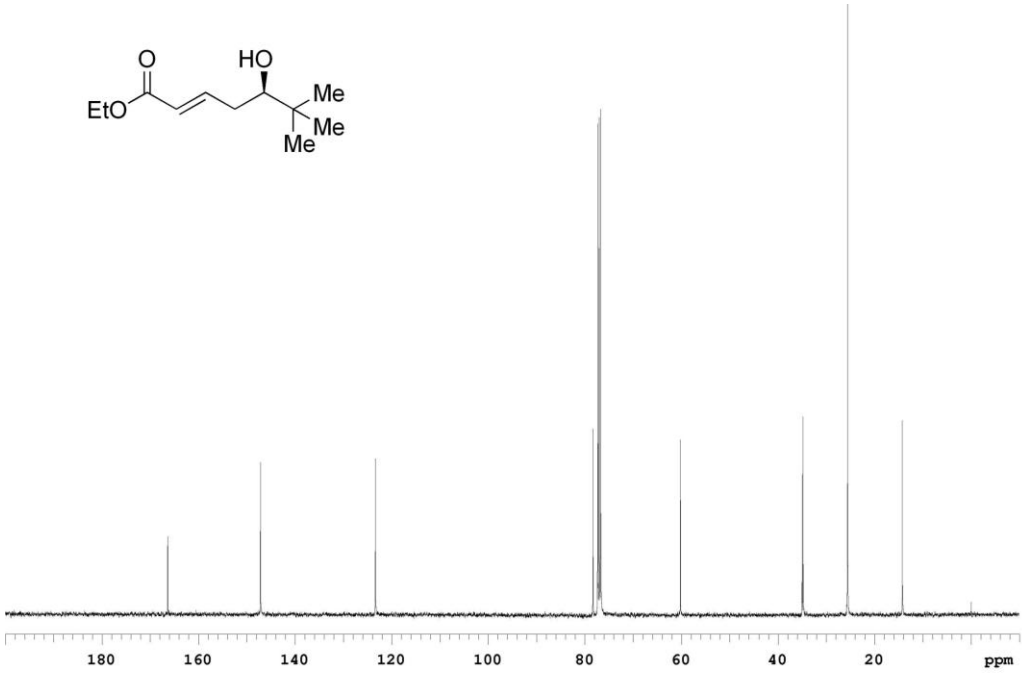
(*R*)-(*E*)-ethyl 5-cyclohexyl-5-hydroxypent-2-enoate (4.60)



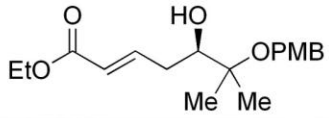


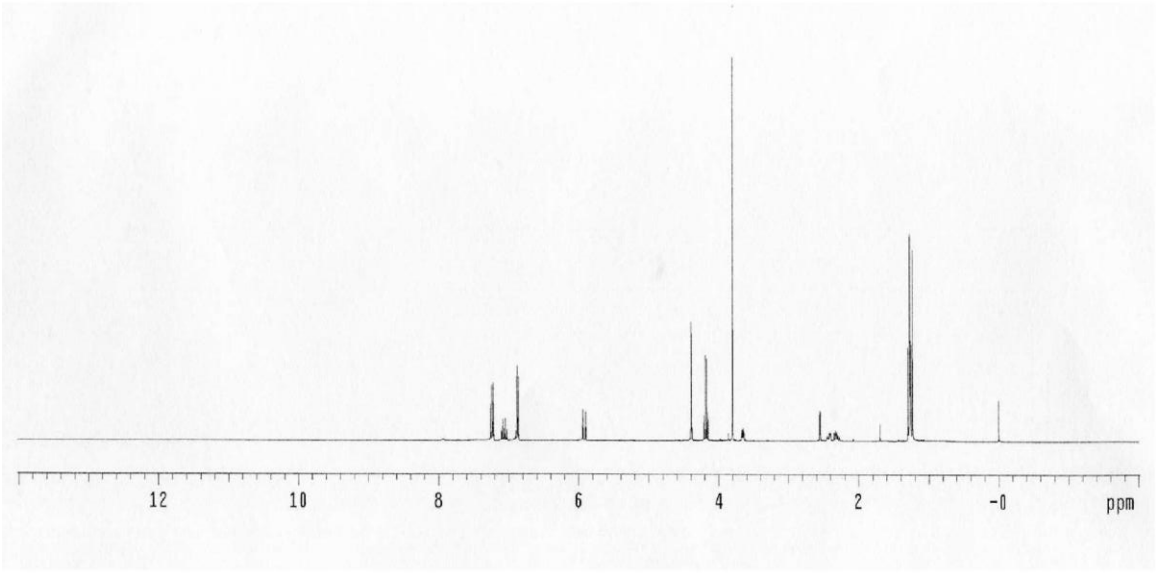
(*R*)-(*E*)-ethyl 5-hydroxy-6,6-dimethylhept-2-enoate (4.62)

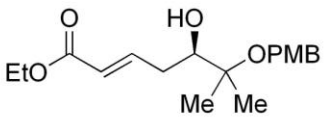


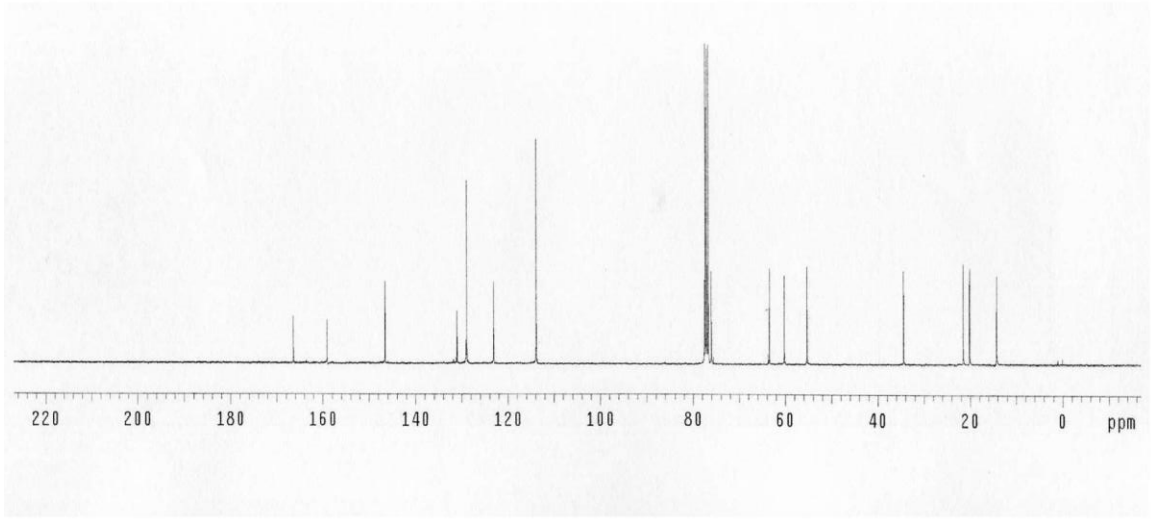


(*R*)-(*E*)-ethyl 5-hydroxy-6-(4-methoxybenzyloxy)-6-methylhept-2-enoate (4.68)

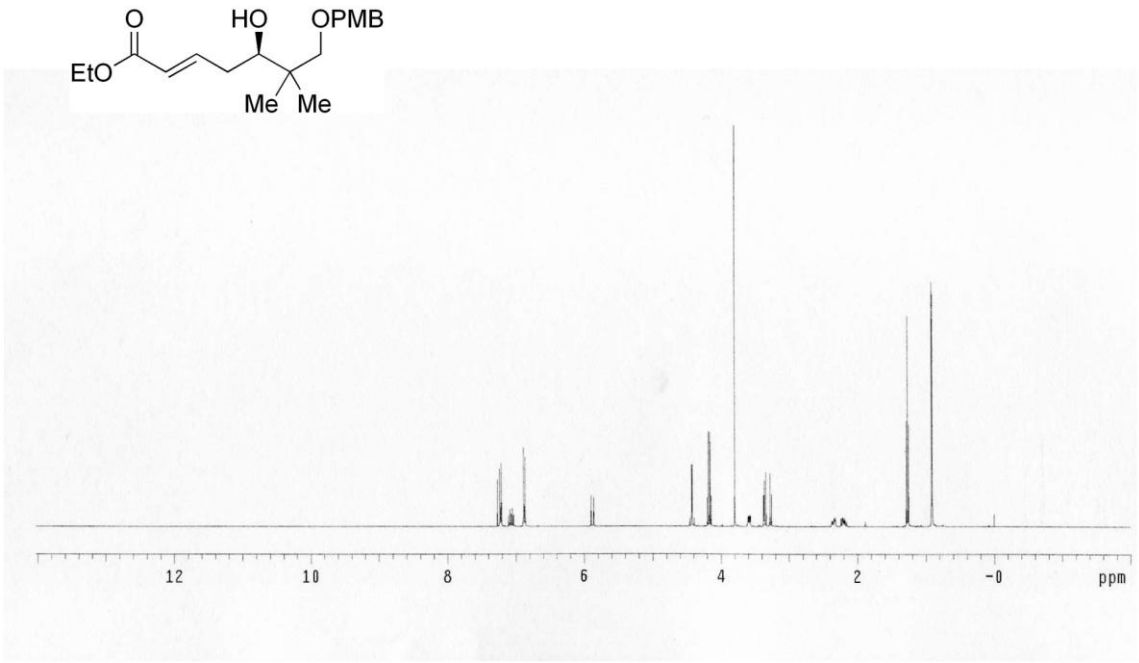


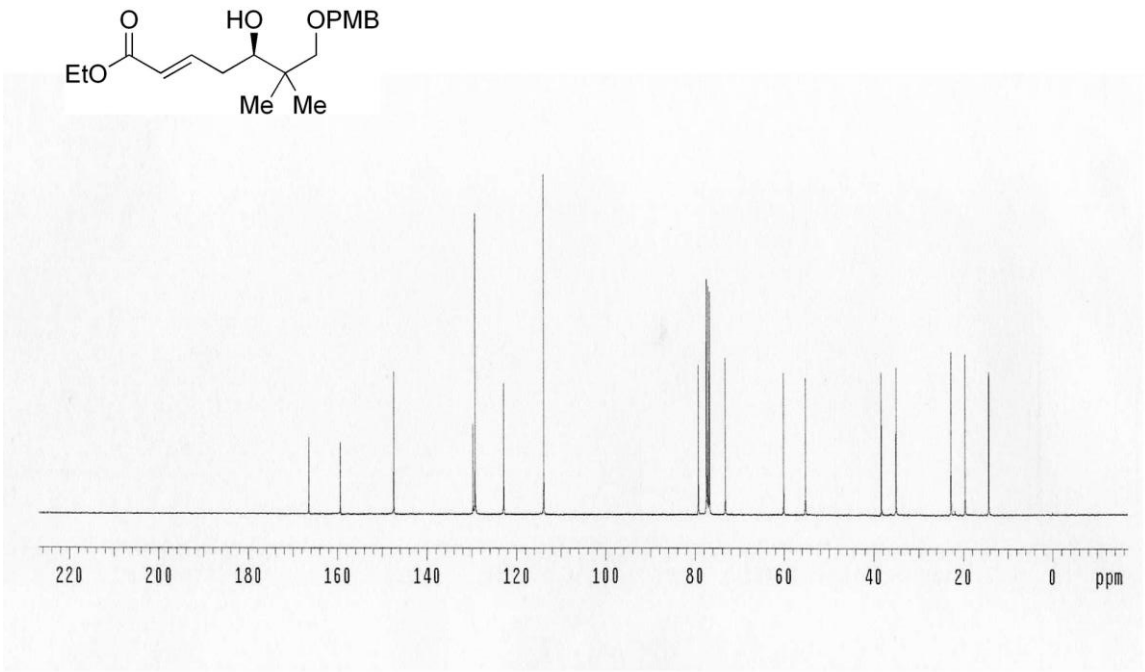




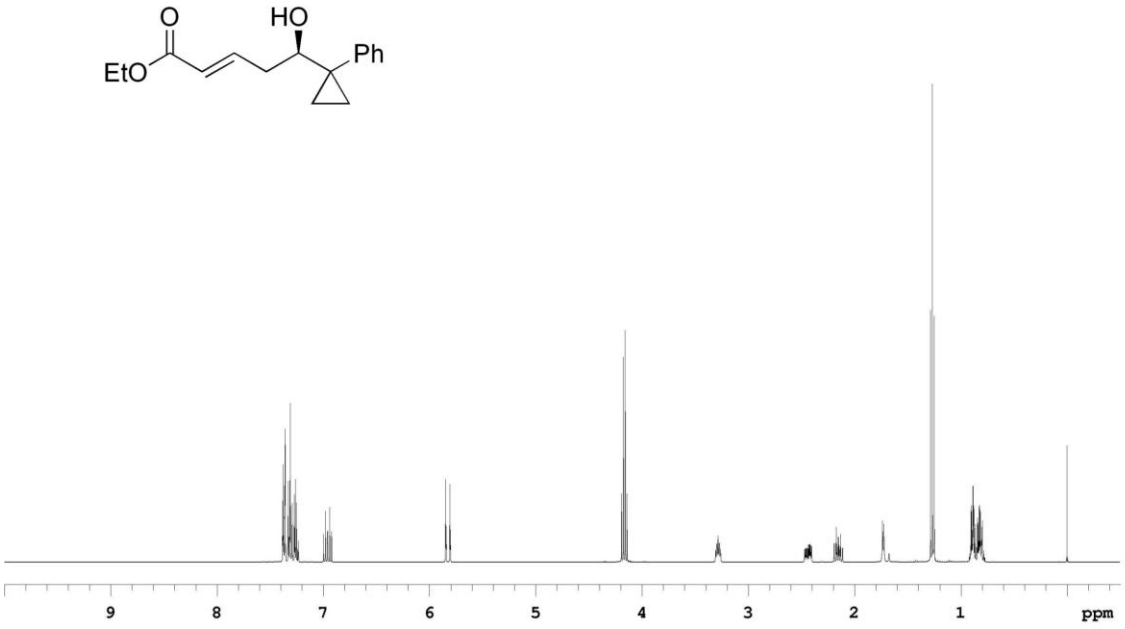


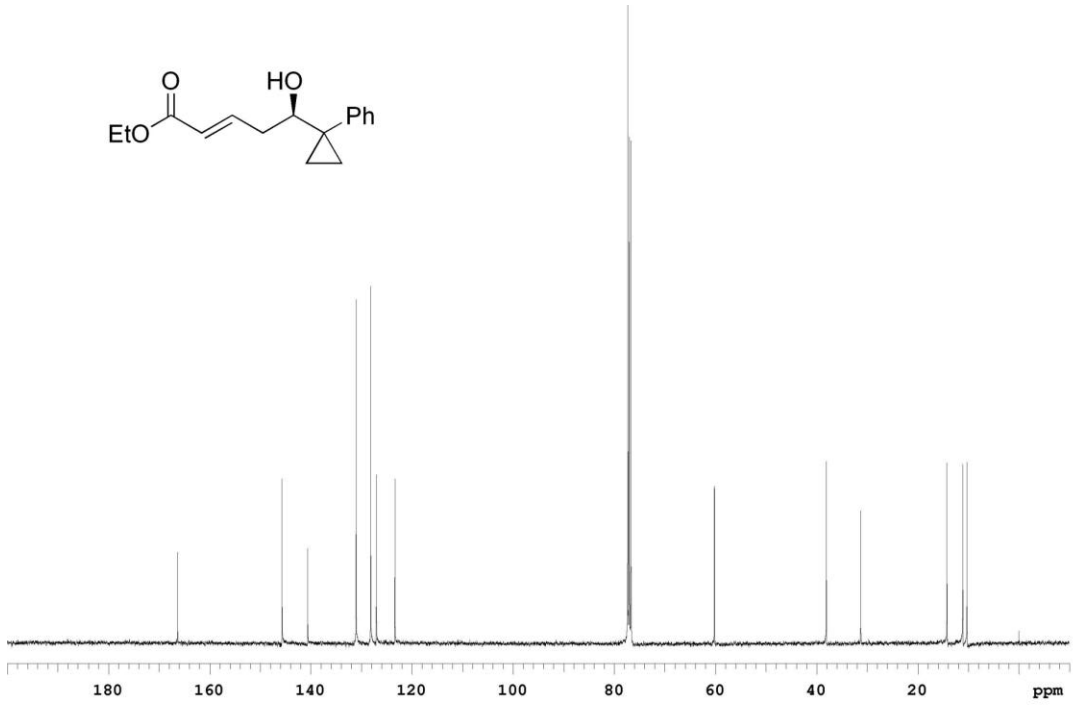
(*R*)-(*E*)-ethyl 5-hydroxy-7-(4-methoxybenzyloxy)-6,6-dimethylhept-2-enoate (4.65)



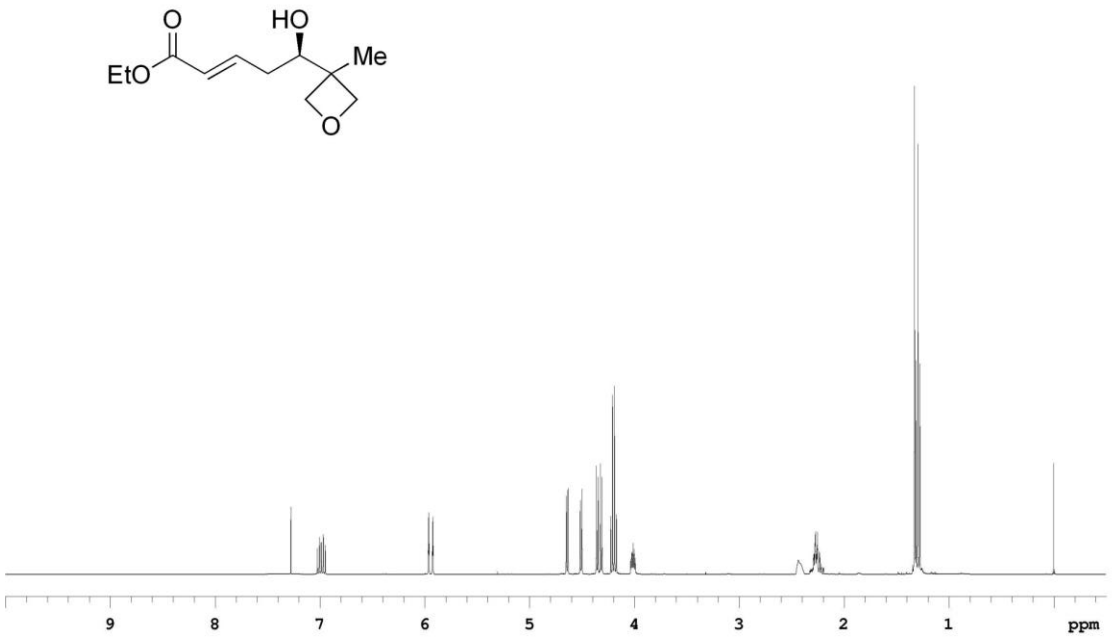


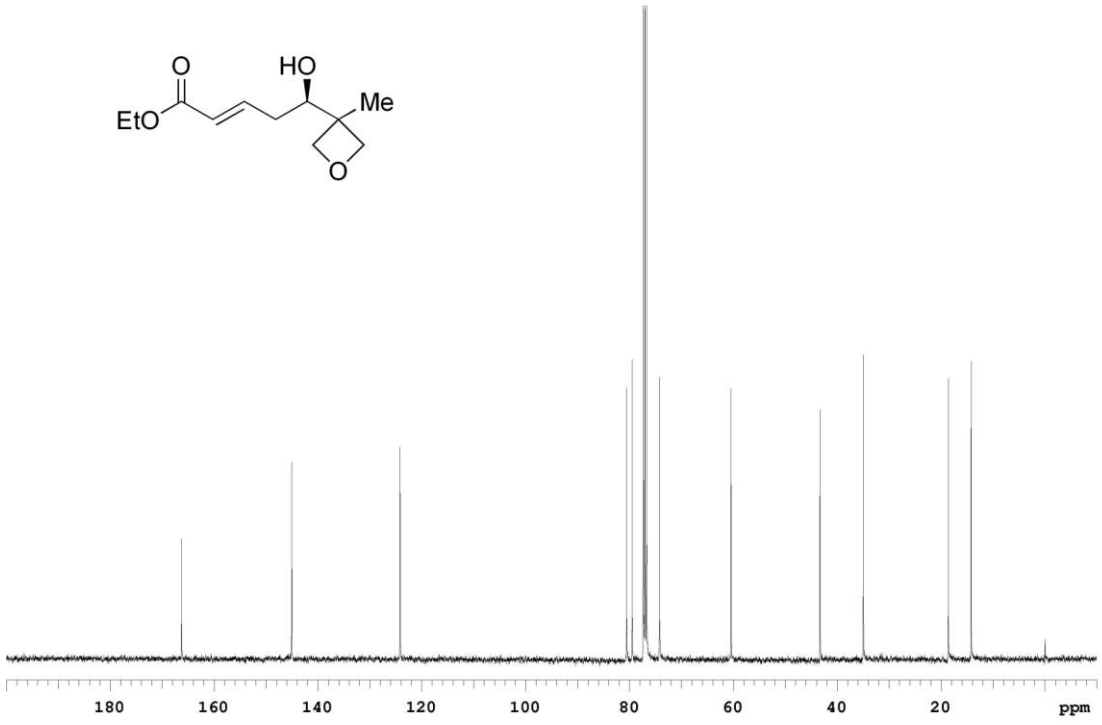
(*R*)-(*E*)-ethyl 5-hydroxy-5-(1-phenylcyclopropyl)pent-2-enoate (4.63)



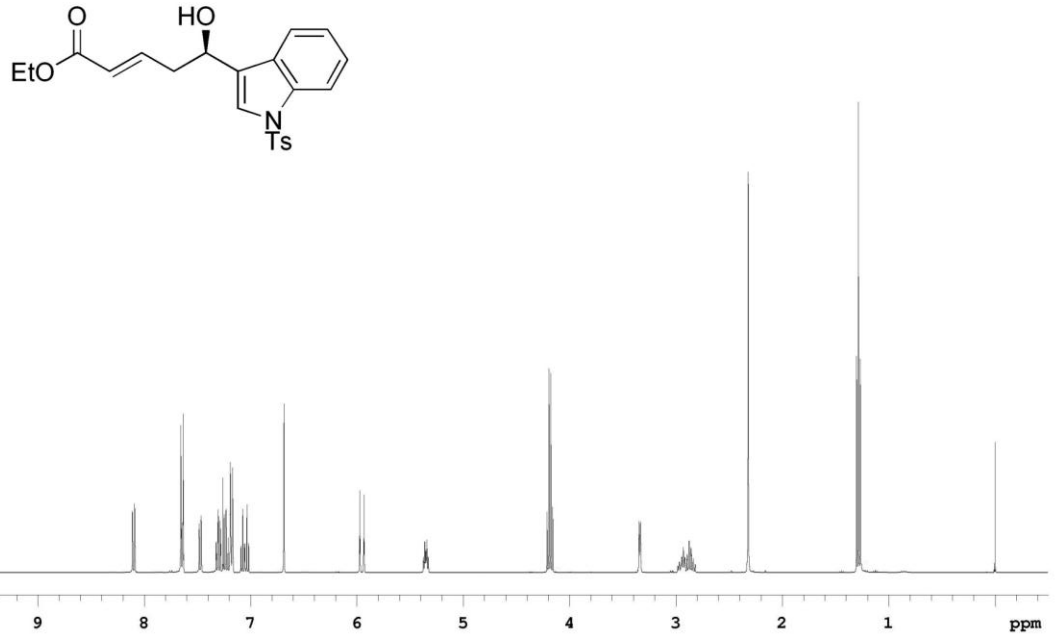


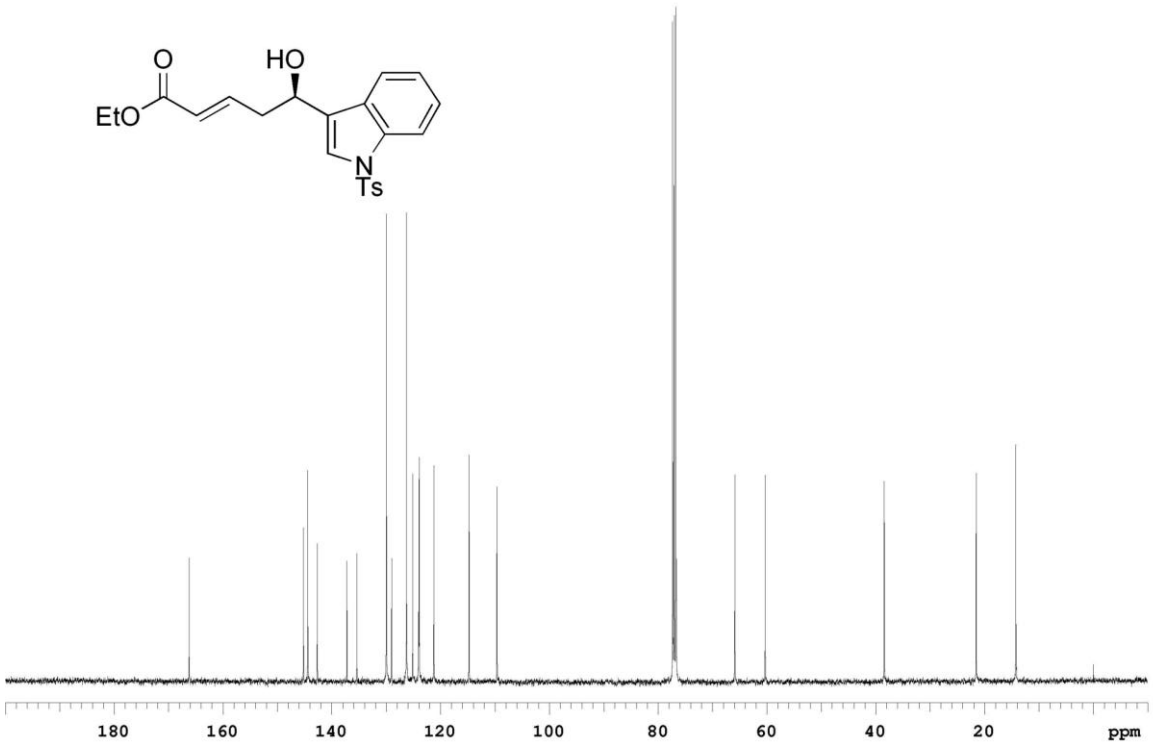
(*R*)-(*E*)-ethyl 5-hydroxy-5-(3-methyloxetan-3-yl)pent-2-enoate (4.66)



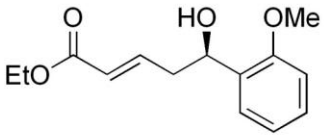


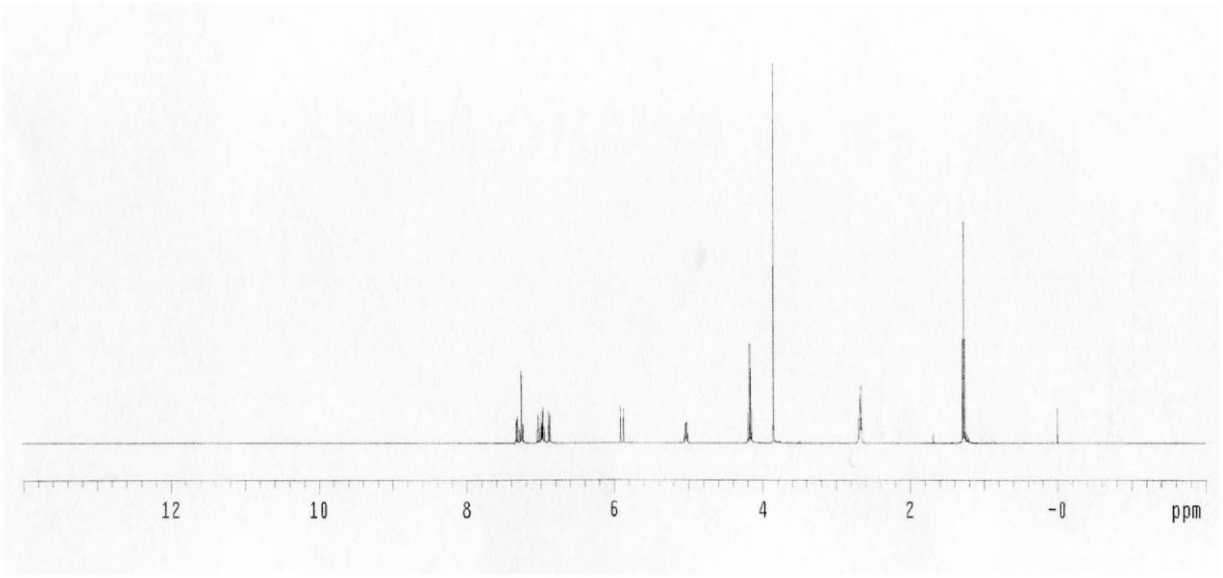
(*R*)-(*E*)-ethyl 5-hydroxy-5-(1-tosyl-1H-indol-3-yl)pent-2-enoate (4.67)

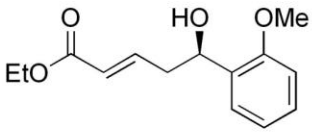


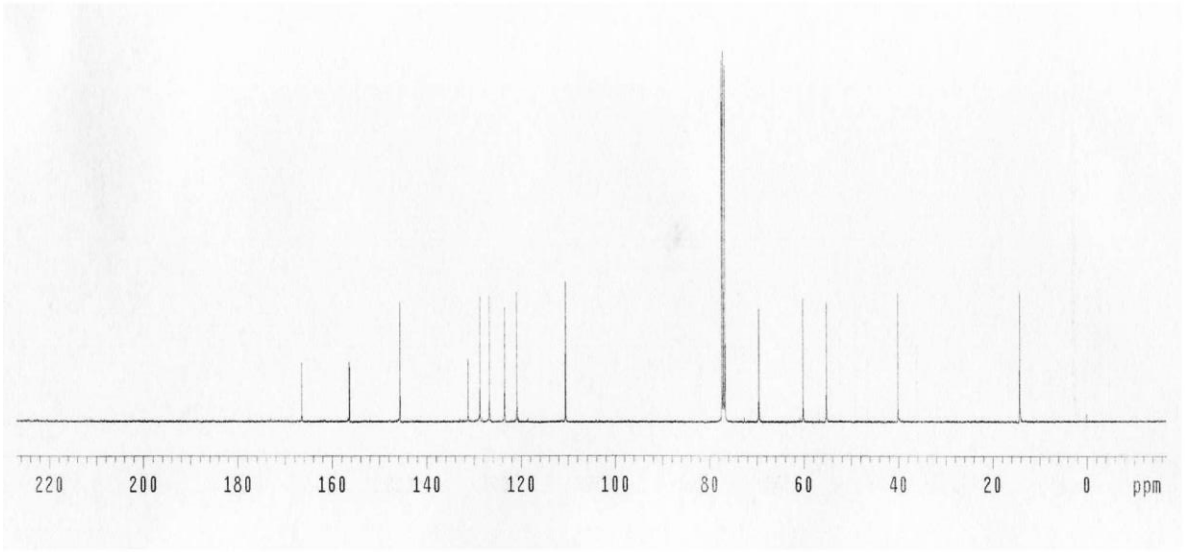


(*R*)-(*E*)-ethyl 5-hydroxy-5-(2-methoxyphenyl)pent-2-enoate (4.64)



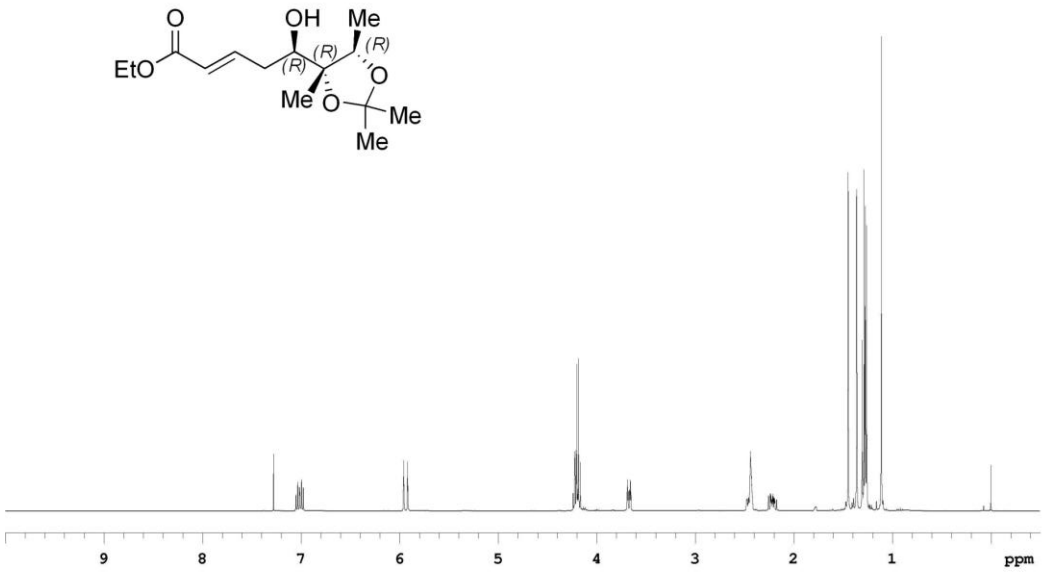


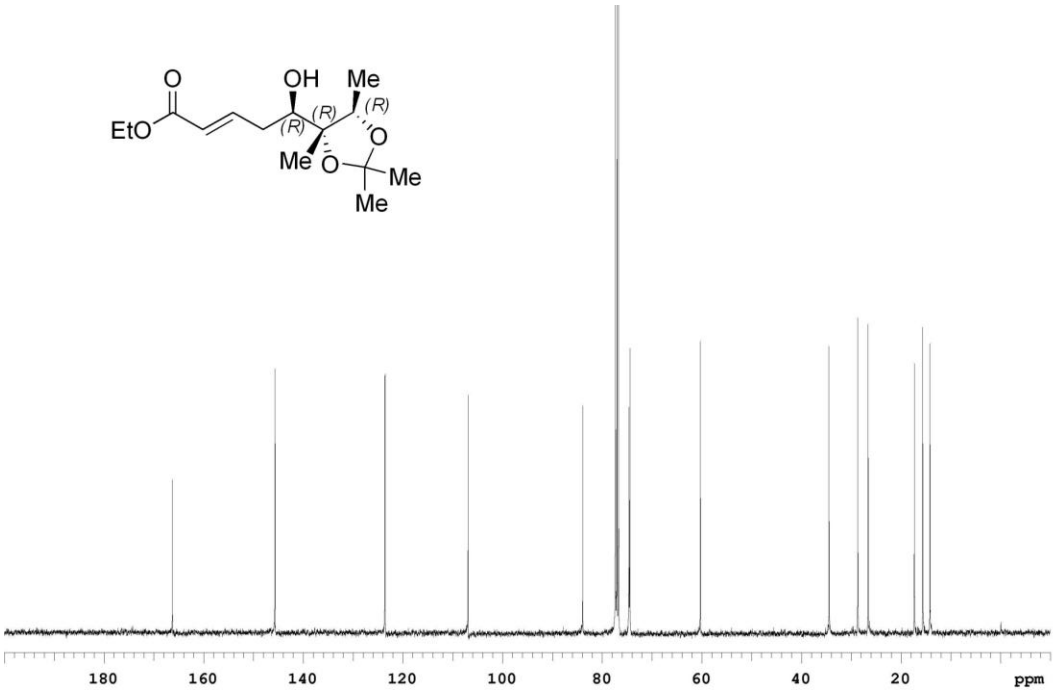




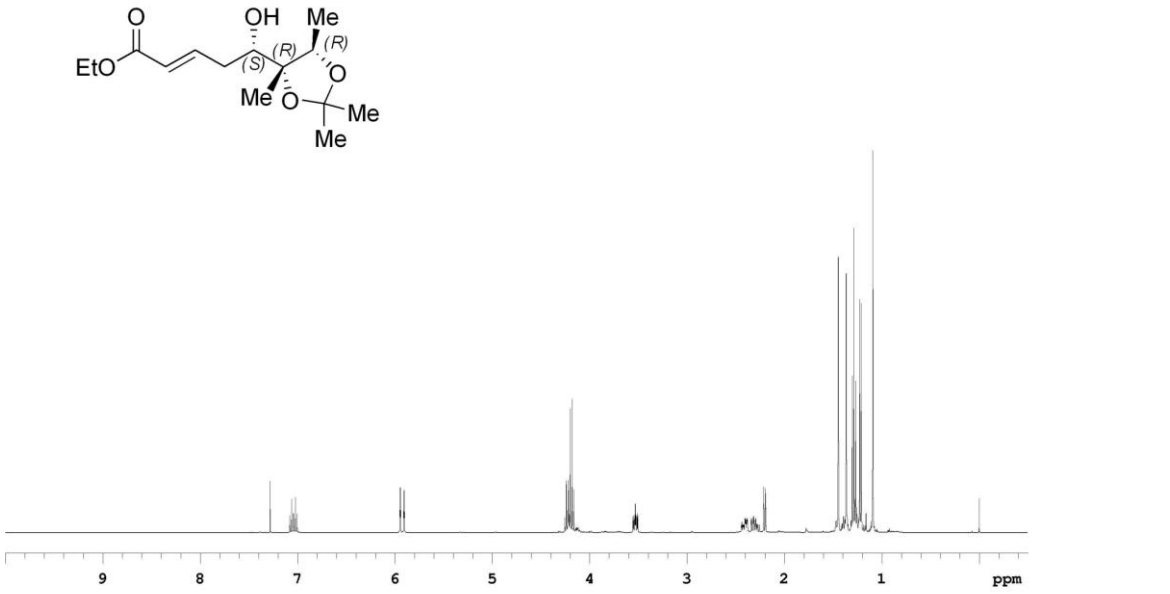
IV Experiment Details Catalyst-Directed Diastereoafacial Selection

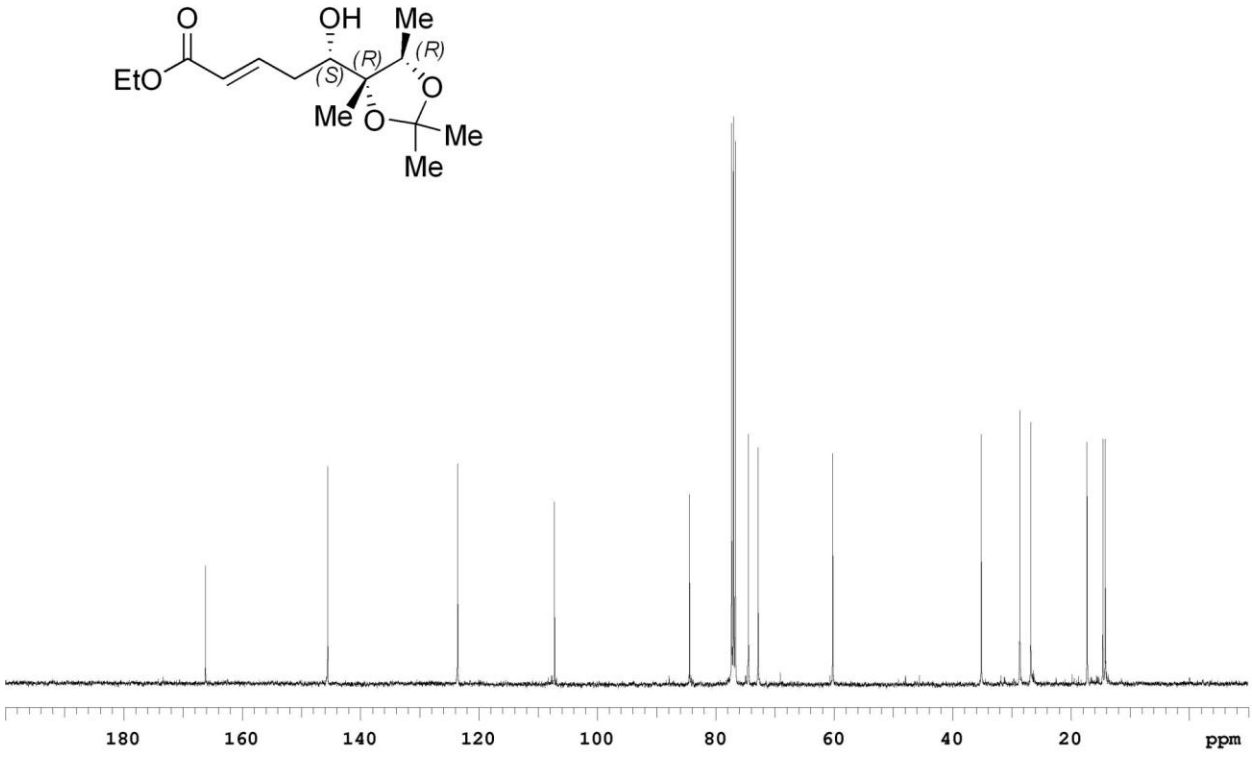
(*R*), (*E*)-ethyl 5-hydroxy-5-[(*4R,5R*)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl]pent-2-enoate (4.71)





(*S*), (*E*)-ethyl 5-hydroxy-5-[(*4R,5R*)-2,2,4,5-tetramethyl-1,3-dioxolan-4-yl]pent-2-enoate (*epi*-4.71)

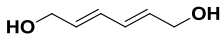


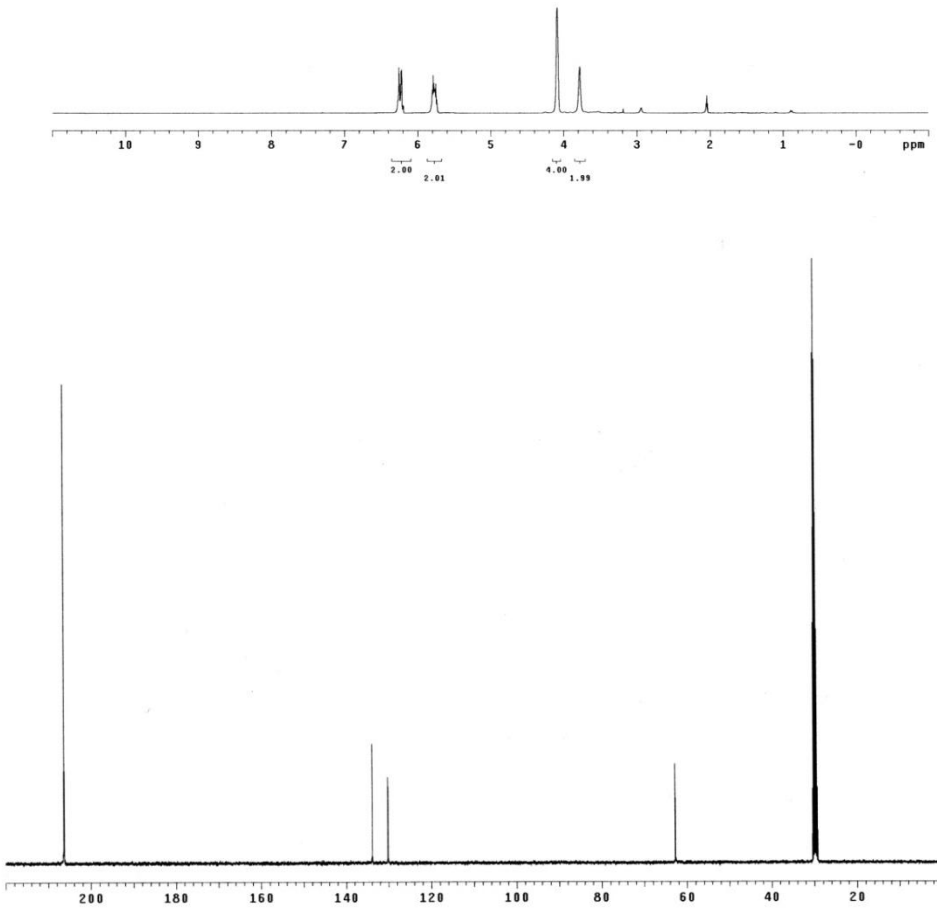


Chapter 5

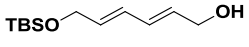
I Fragment A:

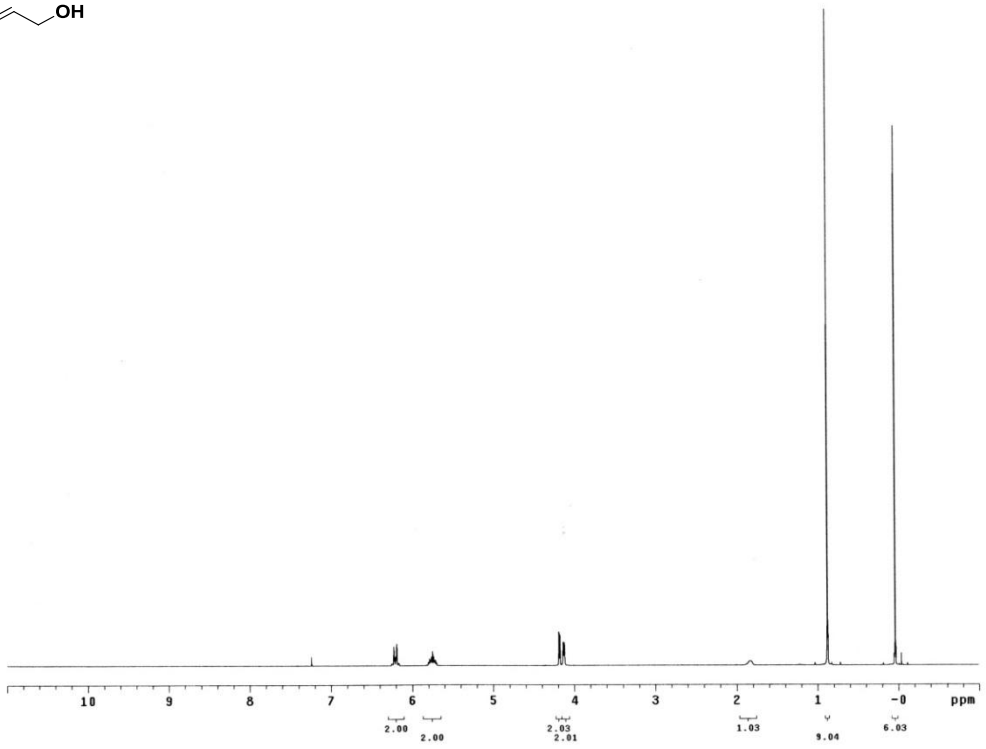
(2*E*,4*E*)-hexa-2,4-diene-1,6-diol (5.6)

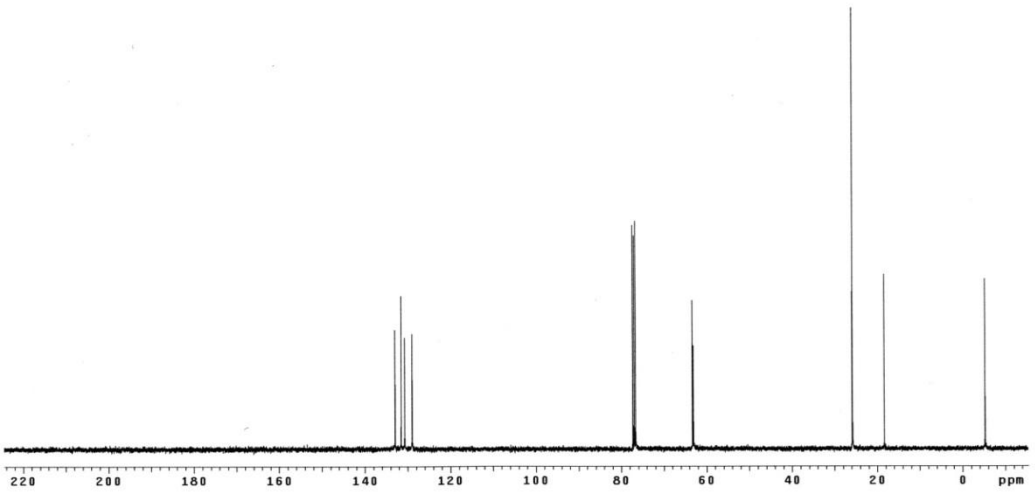




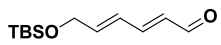
(2*E*,4*E*)-6-(tert-butyldimethylsilyloxy)hexa-2,4-dien-1-ol (5.7)

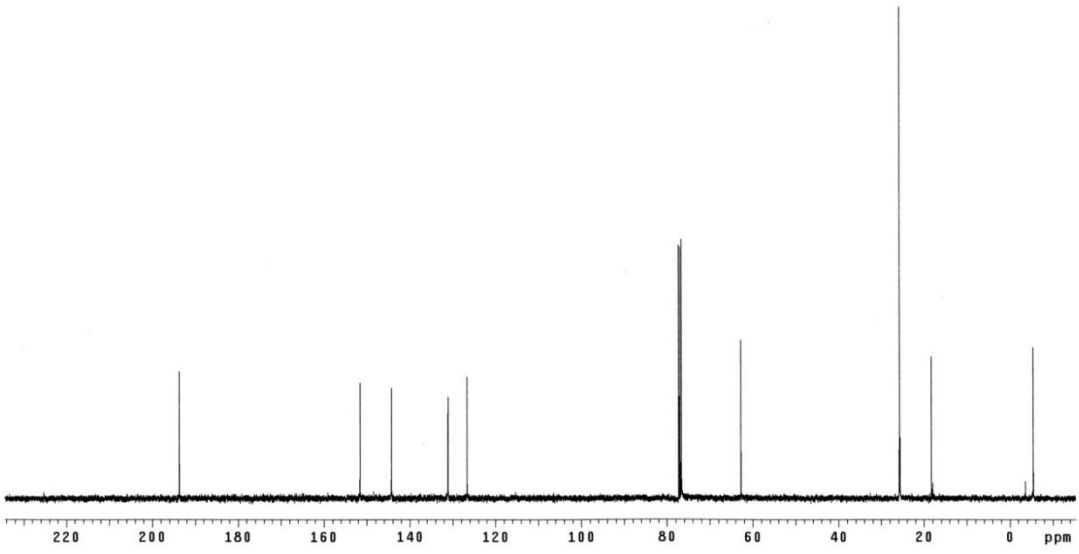




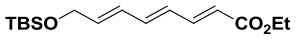


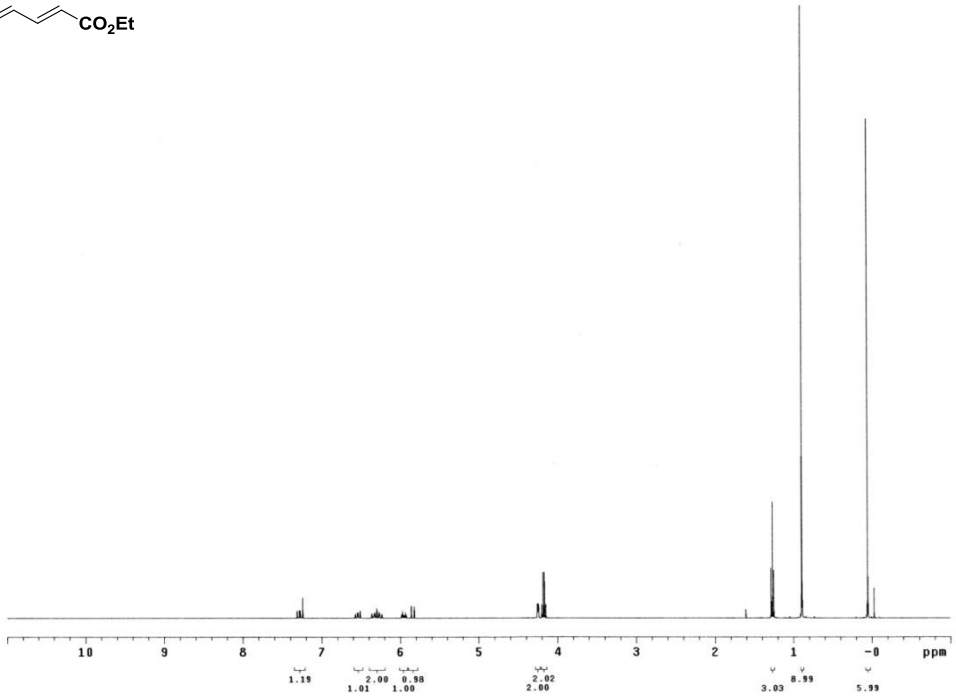
(2*E*,4*E*)-6-(tert-butyldimethylsilyloxy)hexa-2,4-dienal (5.8)

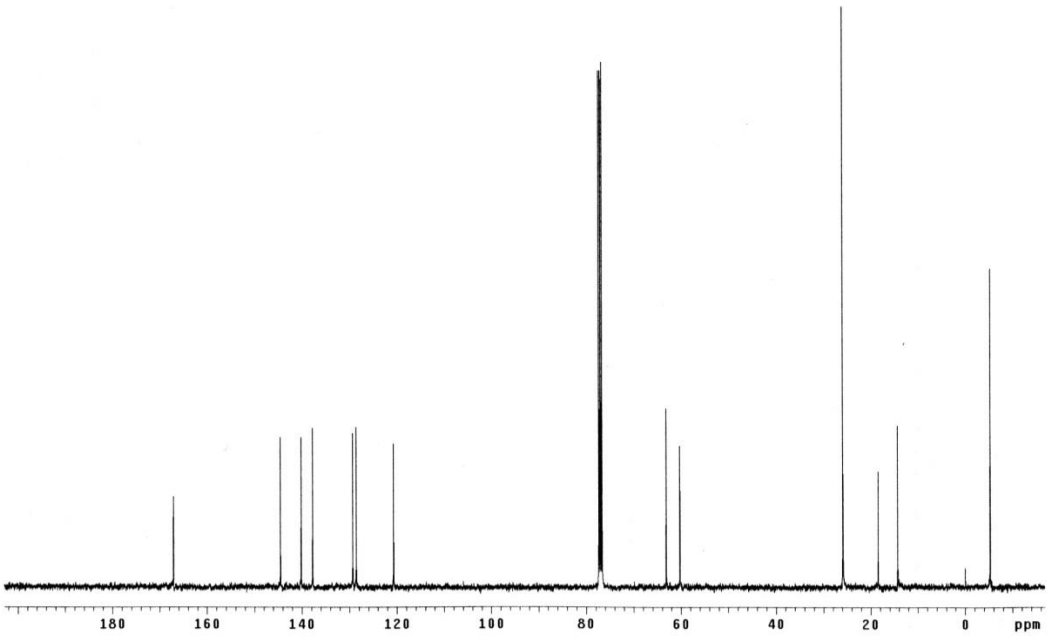




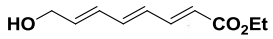
(2*E*,4*E*,6*E*)-ethyl 8-(tert-butyldimethylsilyloxy)octa-2,4,6-trienoate (5.9)

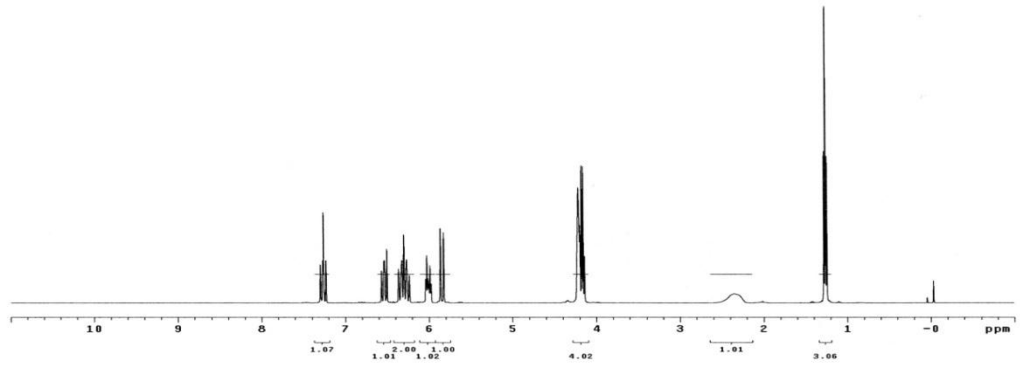


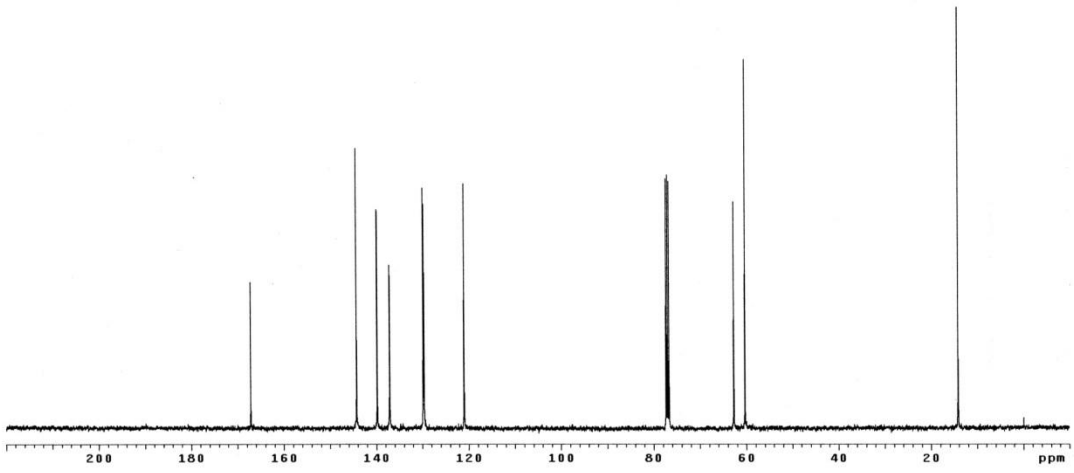




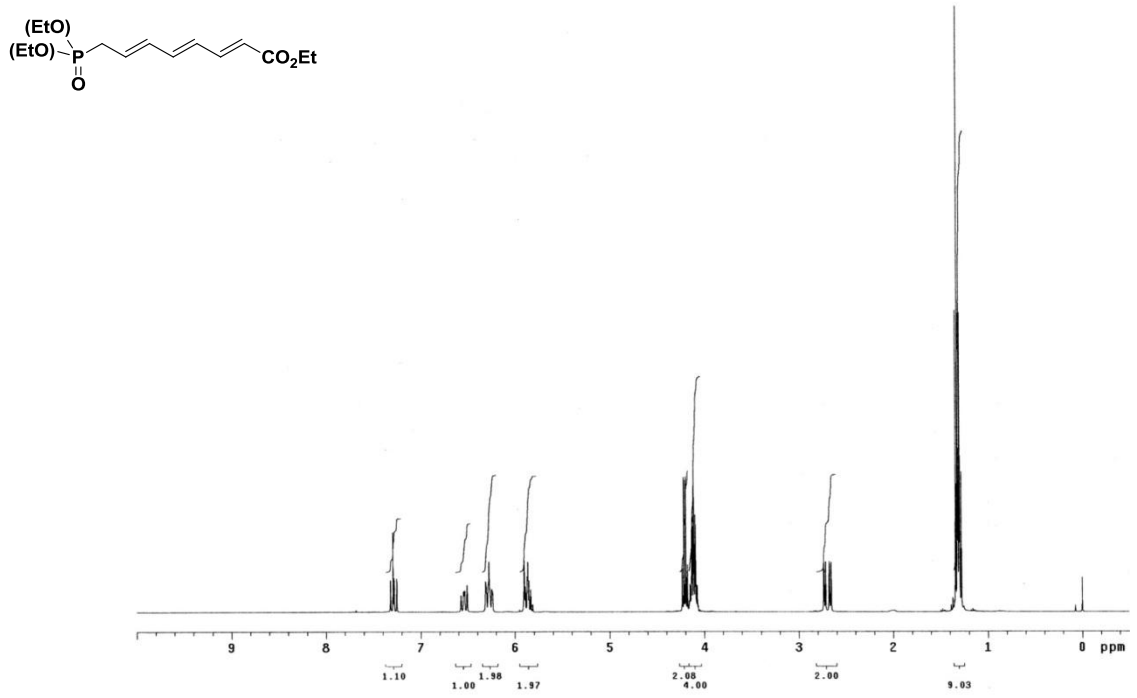
(2*E*,4*E*,6*E*)-ethyl 8-hydroxyocta-2,4,6-trienoate (5.10)

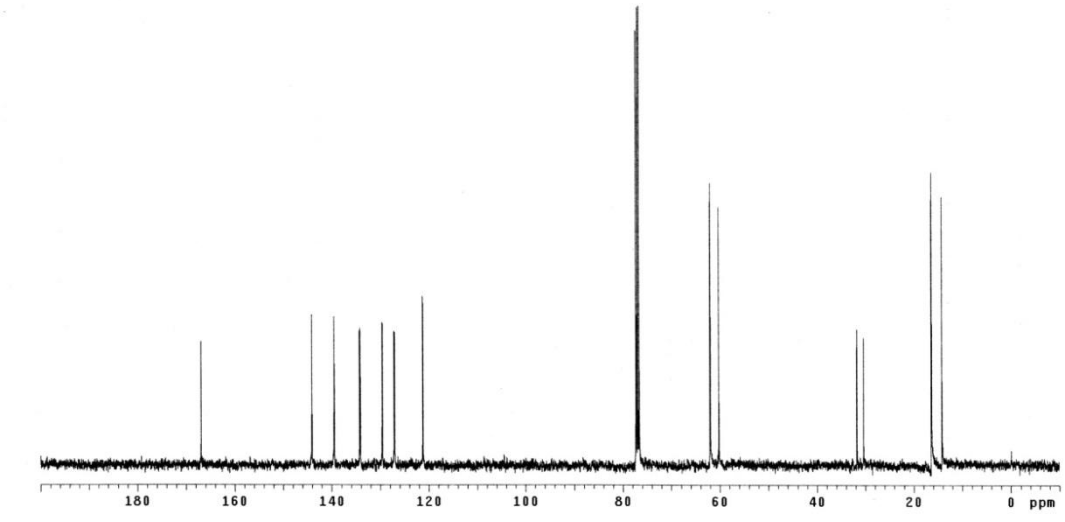






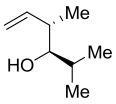
(2E,4E,6E)-ethyl 8-(diethoxyphosphoryl)octa-2,4,6-trienoate (A)

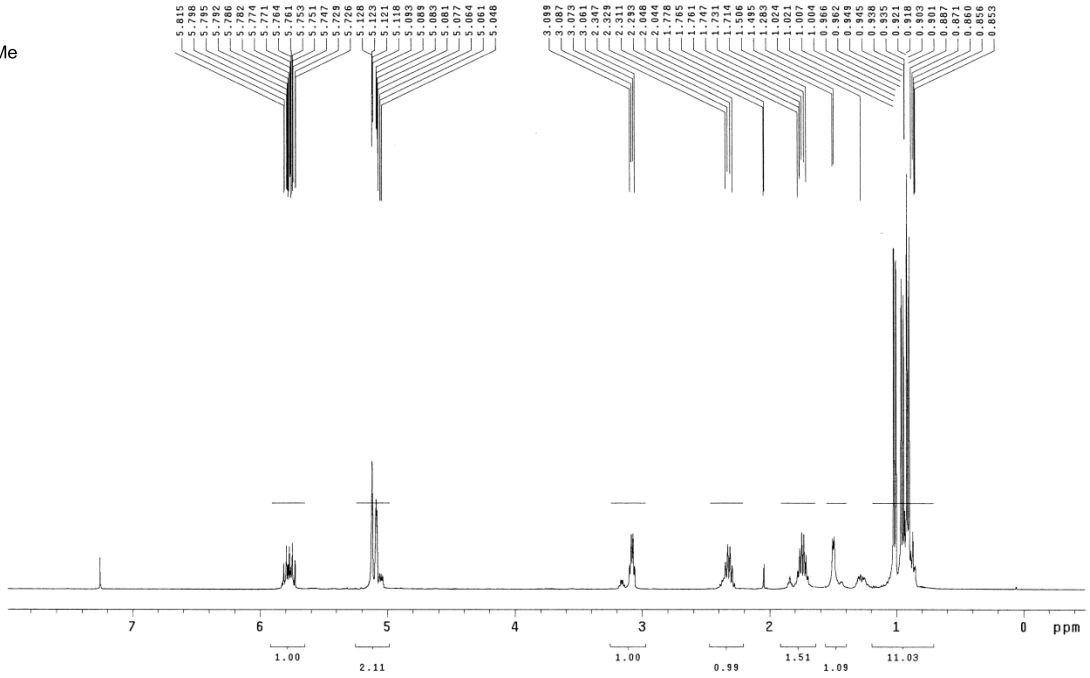


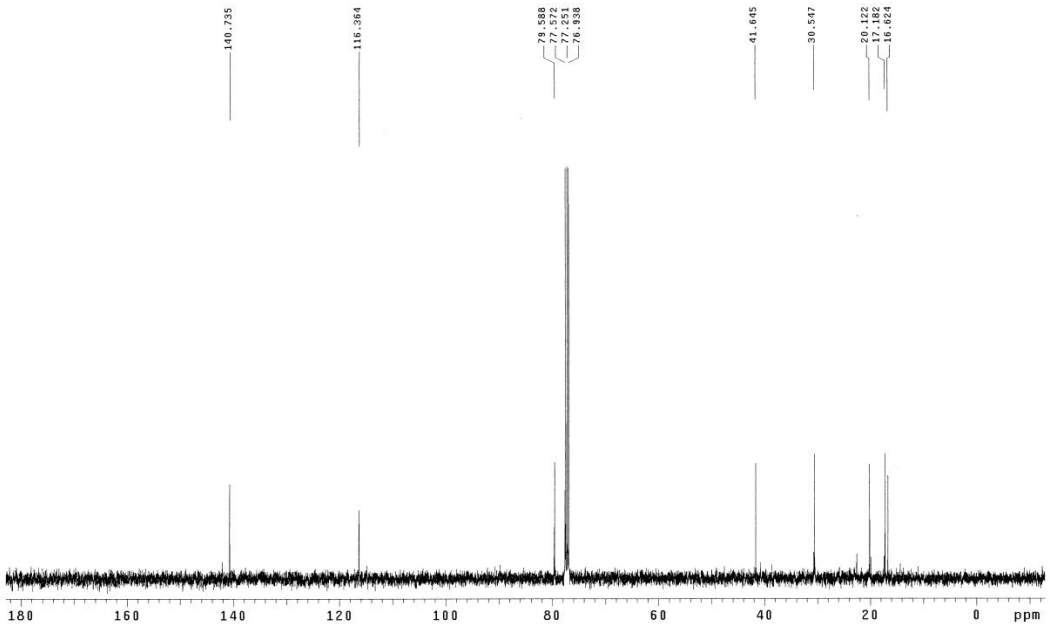


II Fragment B:

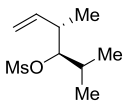
(3*R*,4*S*)-2,4-Dimethylhex-5-en-3-ol (5.14)

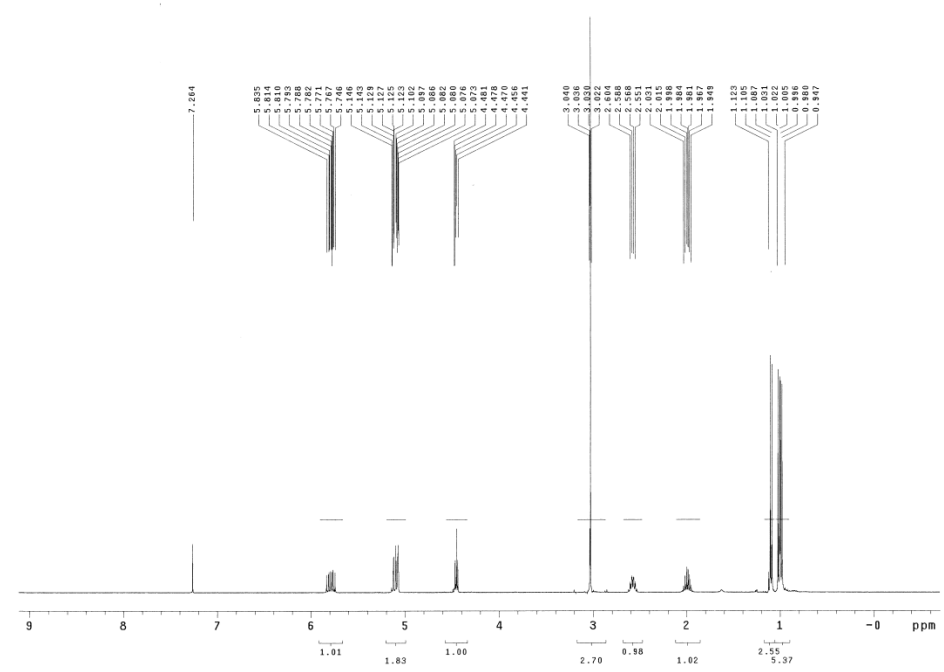


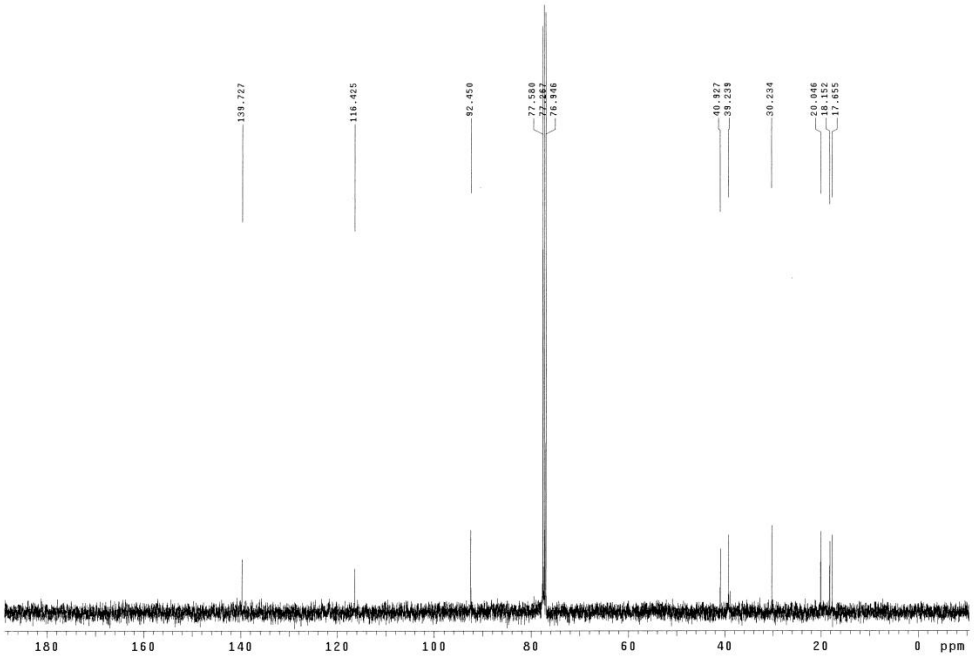




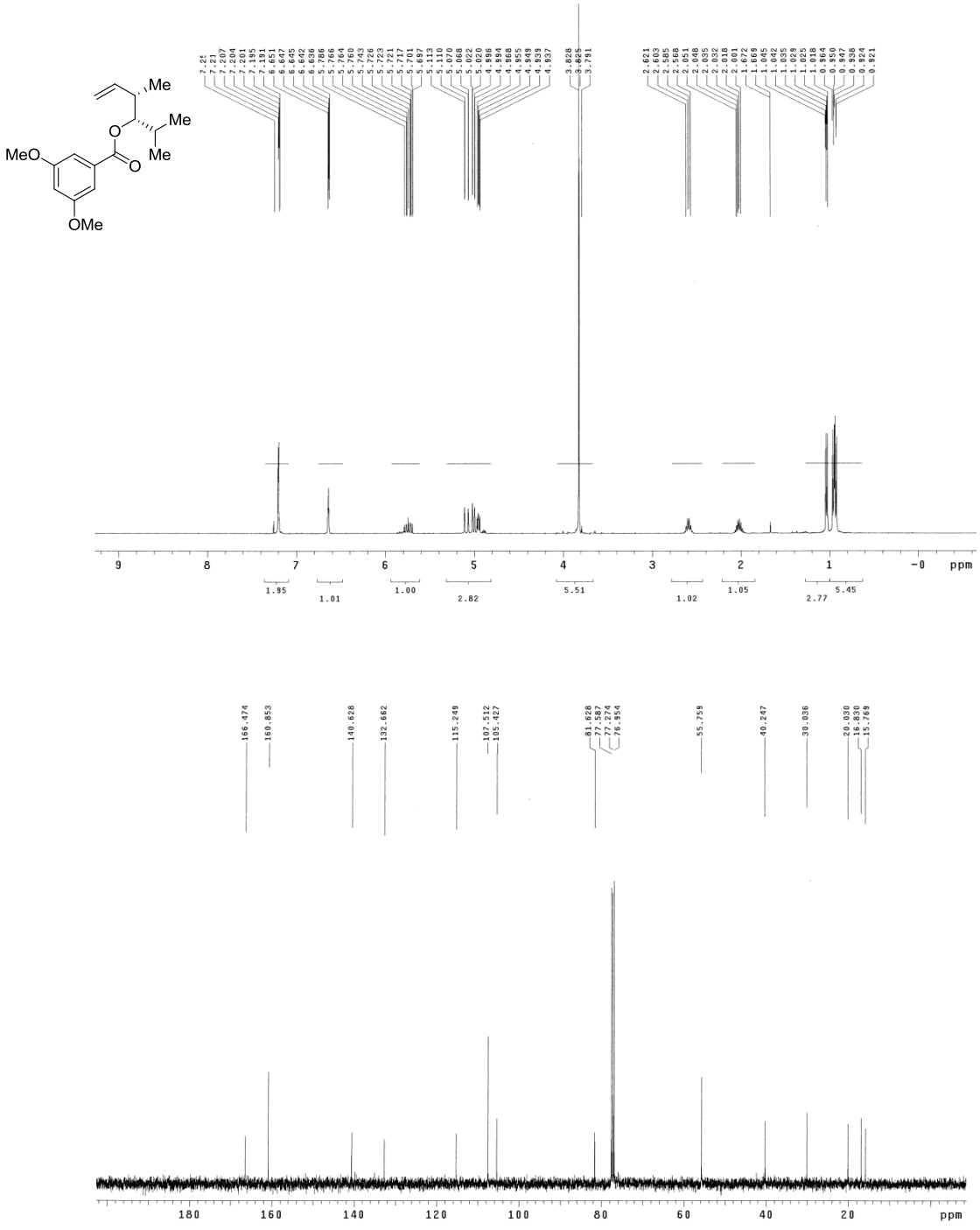
(3*R*,4*S*)-2,4-Dimethylhex-5-en-3-yl methanesulfonate (5.15)



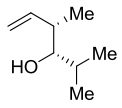


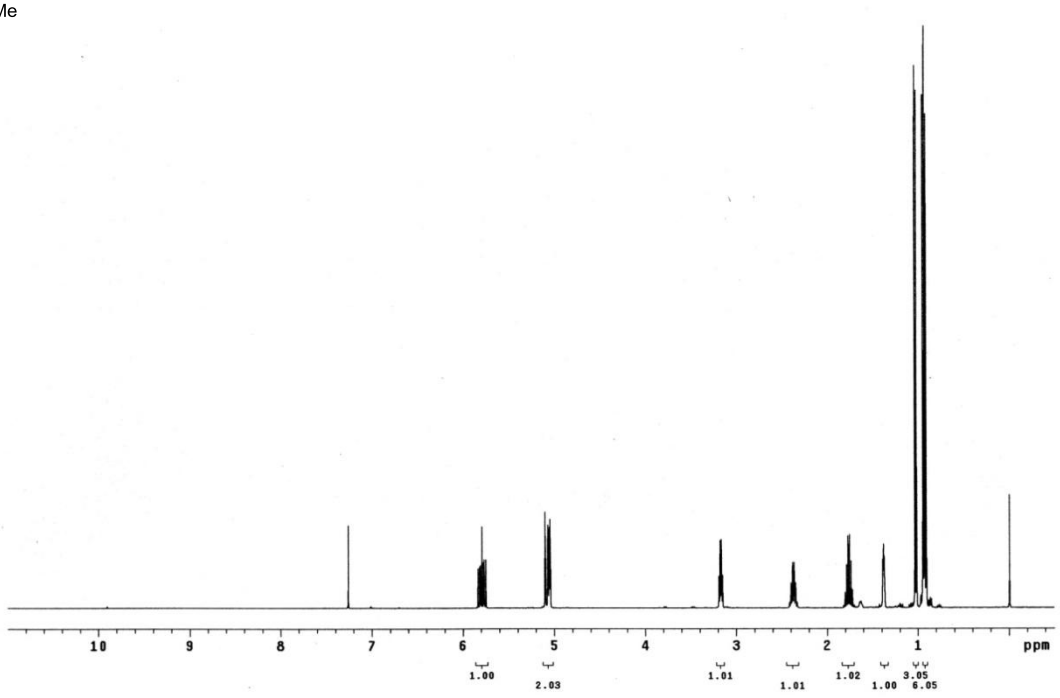


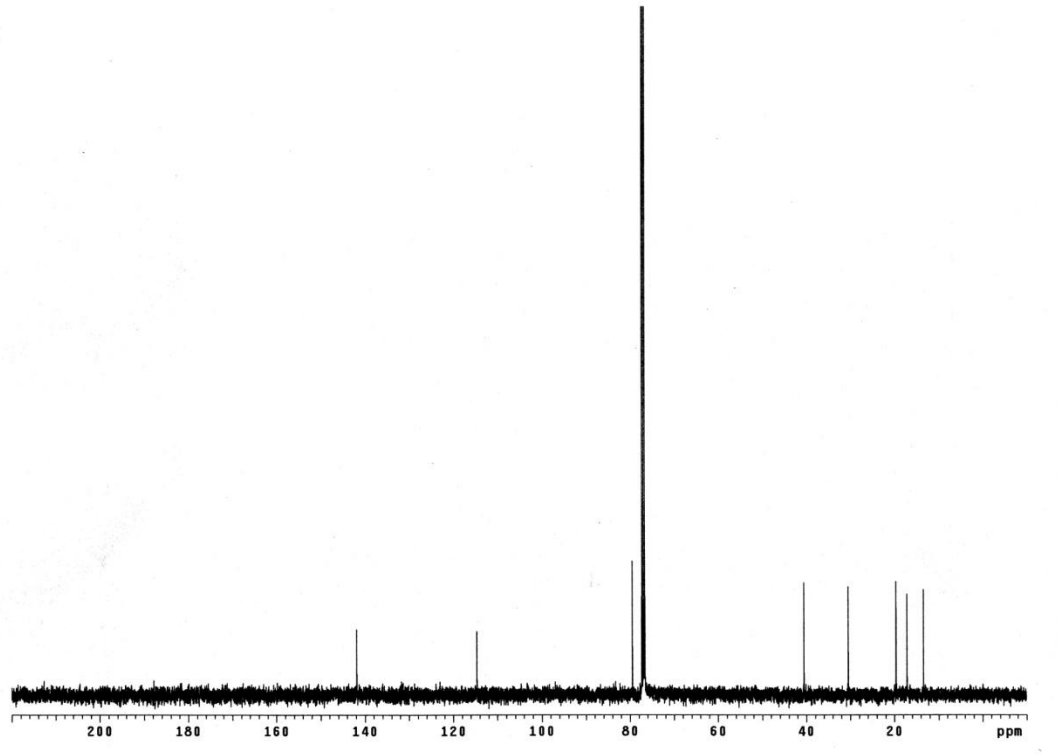
(3*S*,4*S*)-2,4-Dimethylhex-5-en-3-yl 3,5-dimethoxybenzoate (5.16)



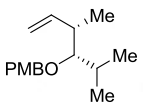
(3*S*,4*S*)-2,4-dimethylhex-5-en-3-ol (5.17)

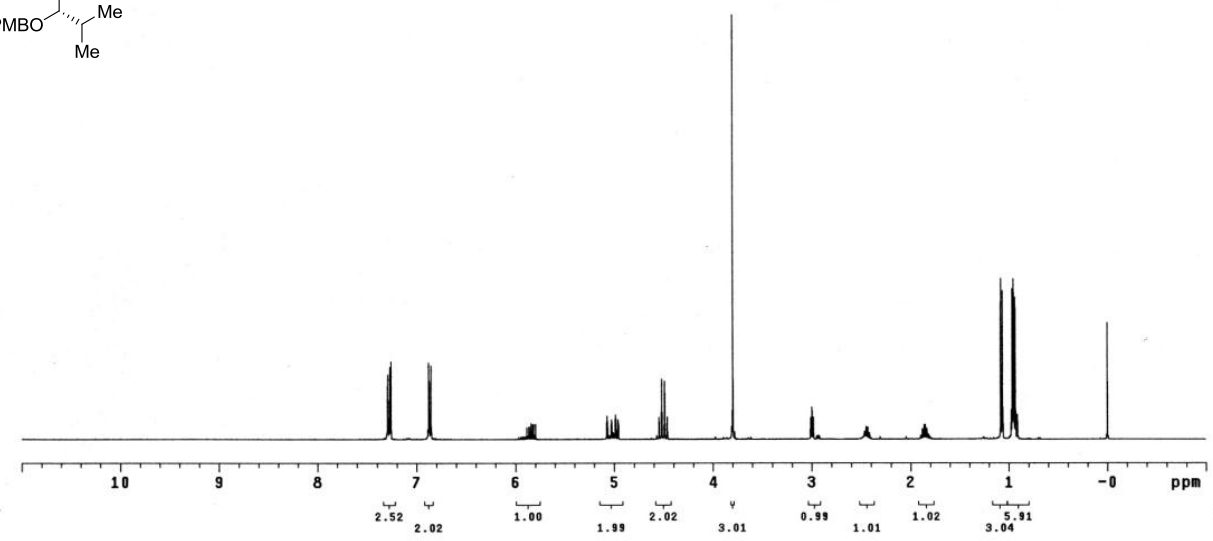


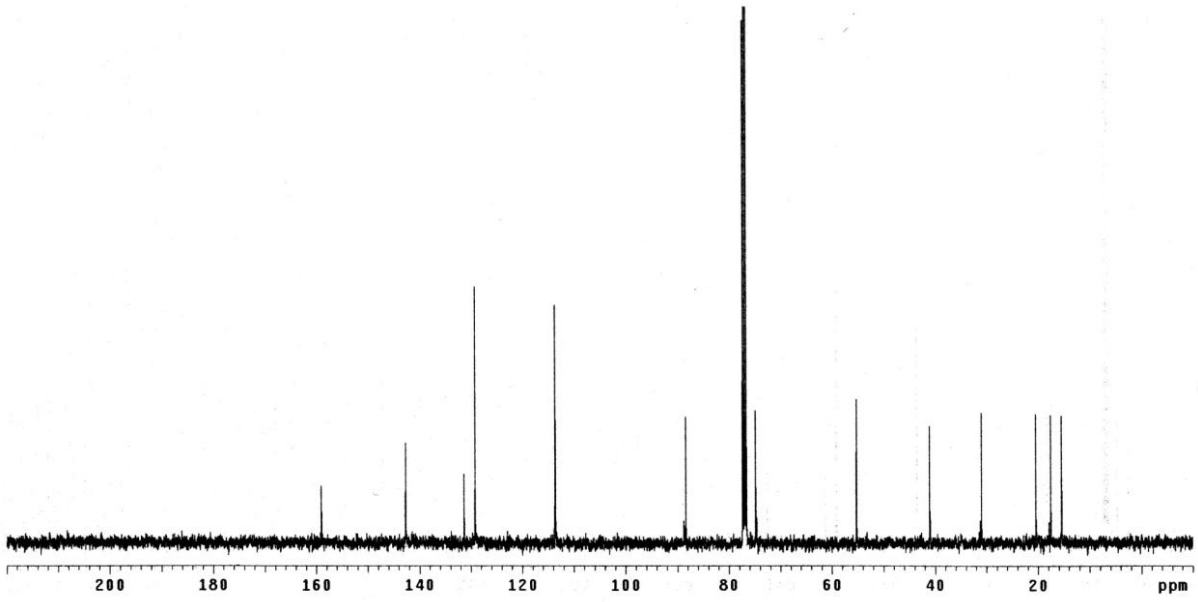




1-(((3*S*,4*S*)-2,4-dimethylhex-5-en-3-yloxy)methyl)-4-methoxybenzene (5.18, B)

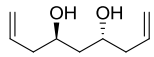


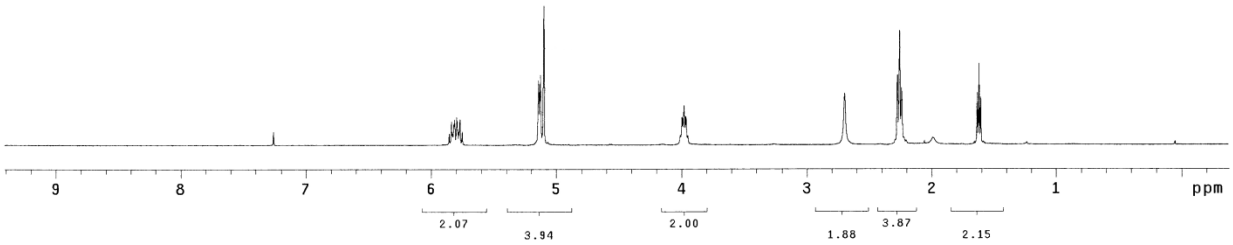


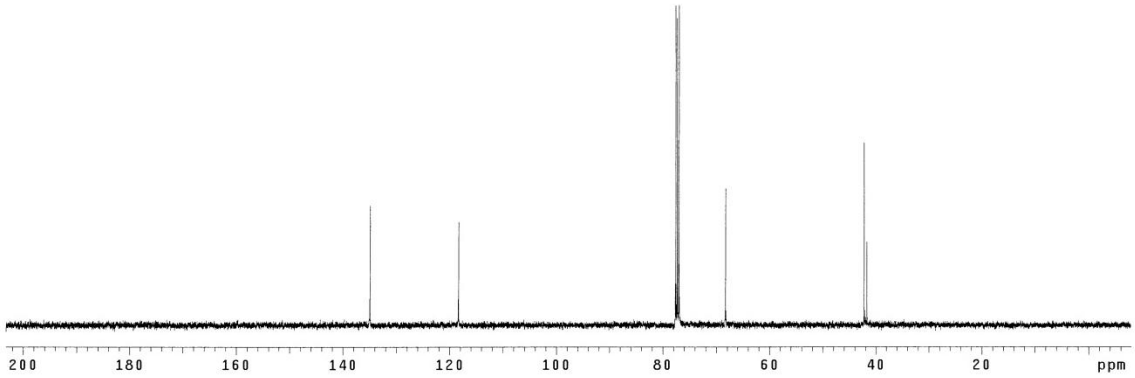


III Fragment C:

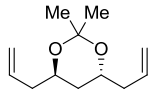
(4*R*,6*R*)-Nona-1,8-diene-4,6-diol (5.32)

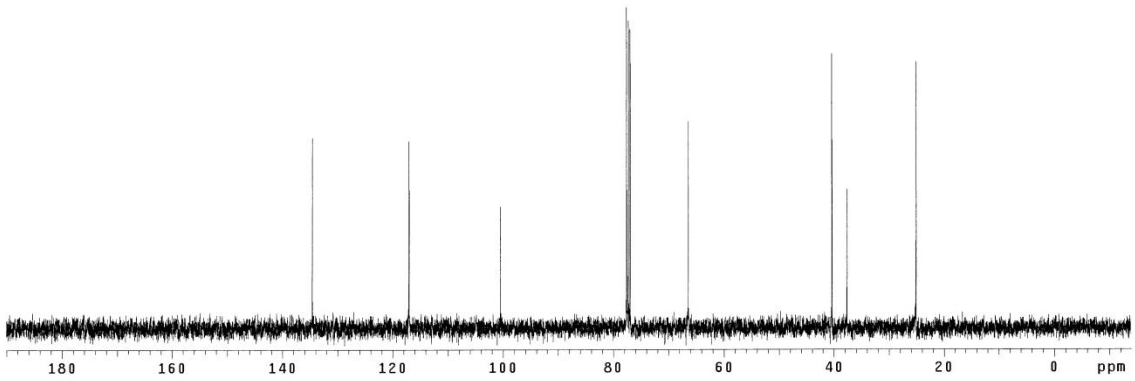




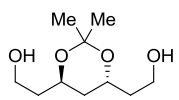


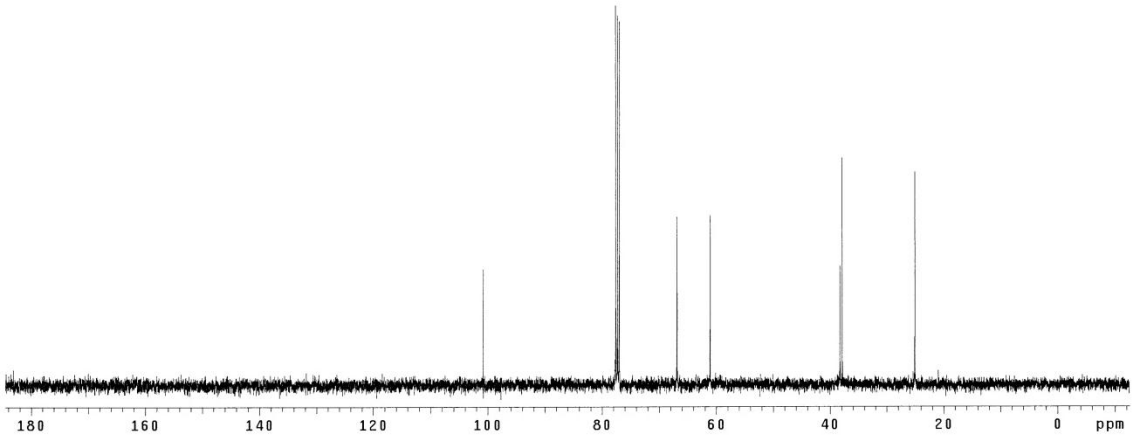
(4*R*,6*R*)-4,6-Diallyl-2,2-dimethyl-1,3-dioxane (5.33)



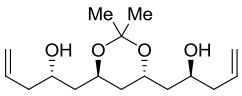


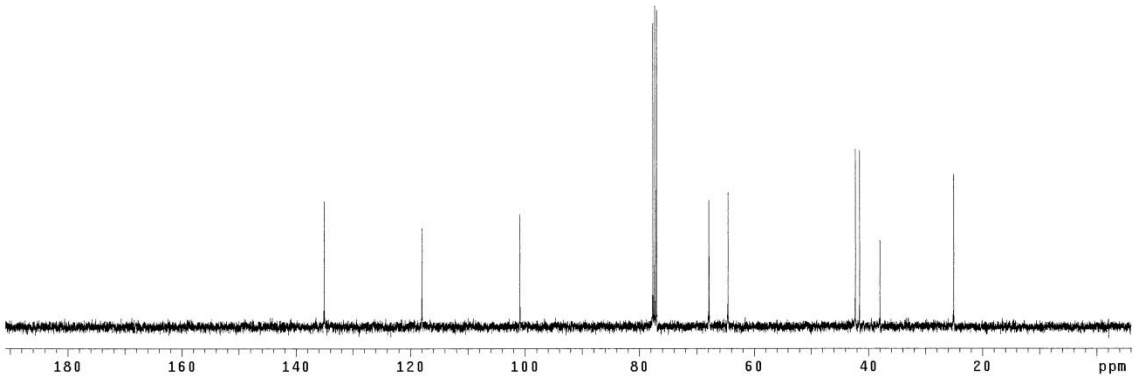
2,2'-((4*R*,6*R*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)diethanol (5.34)



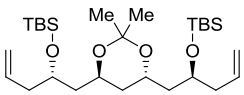


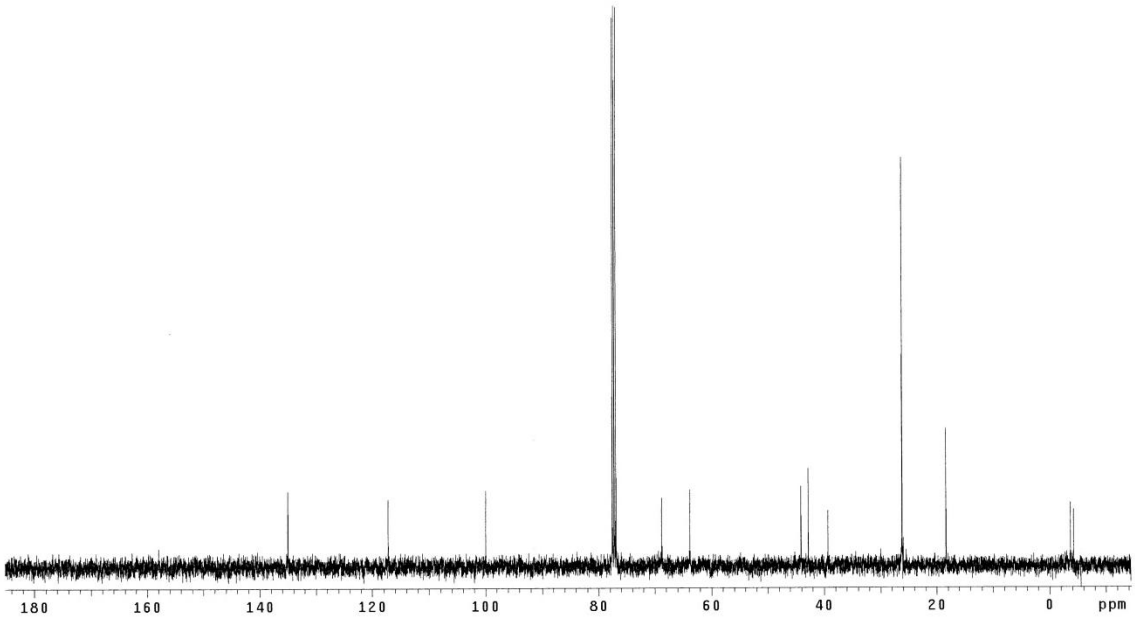
(2*S*,2'*S*)-1,1'-((4*R*,6*R*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)dipent-4-en-2-ol (5.35)



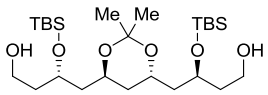


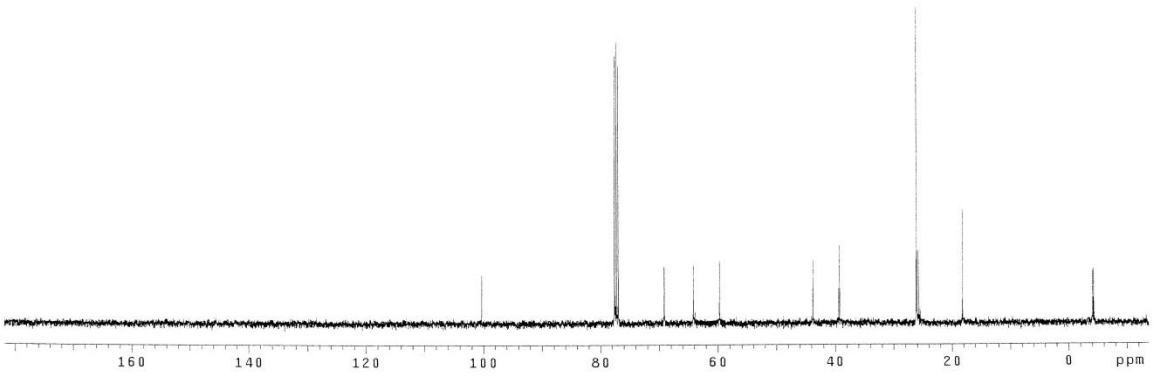
(2*S*,2'*S*)-1,1'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(pent-4-ene-2,1 diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (5.36)



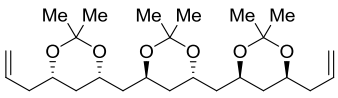


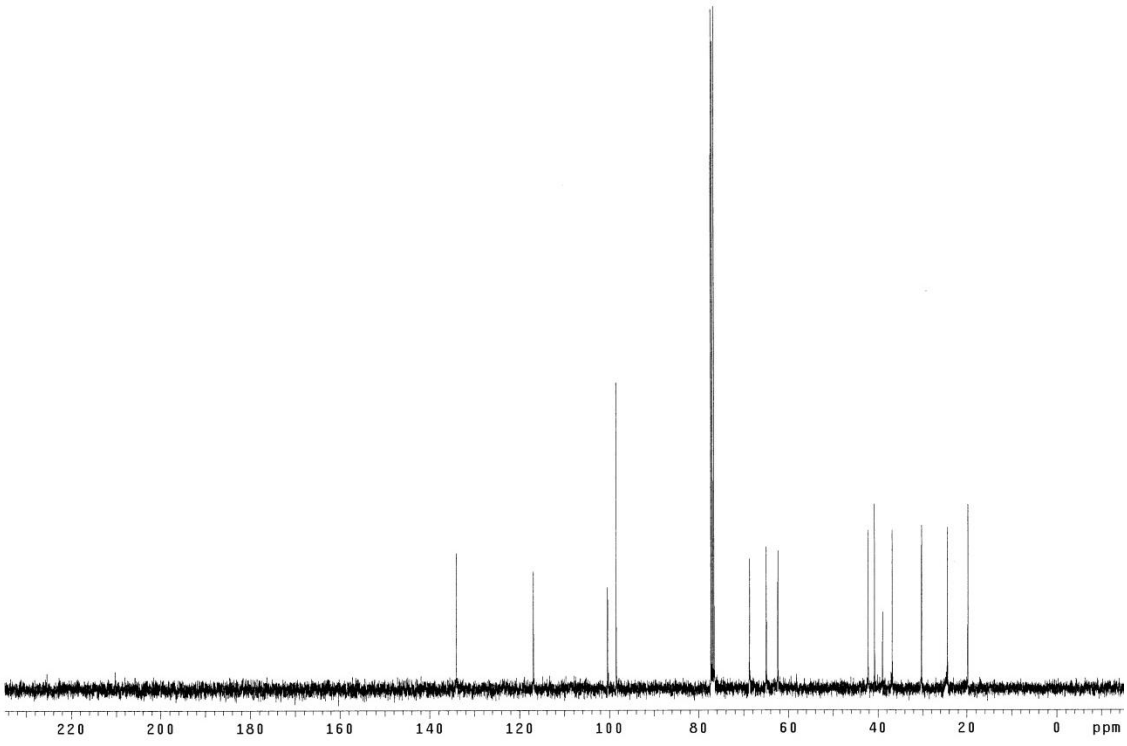
(3*S*,3'*S*)-4,4'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(3-(*tert*-butyldimethylsilyloxy)butan-1-ol) (5.37)



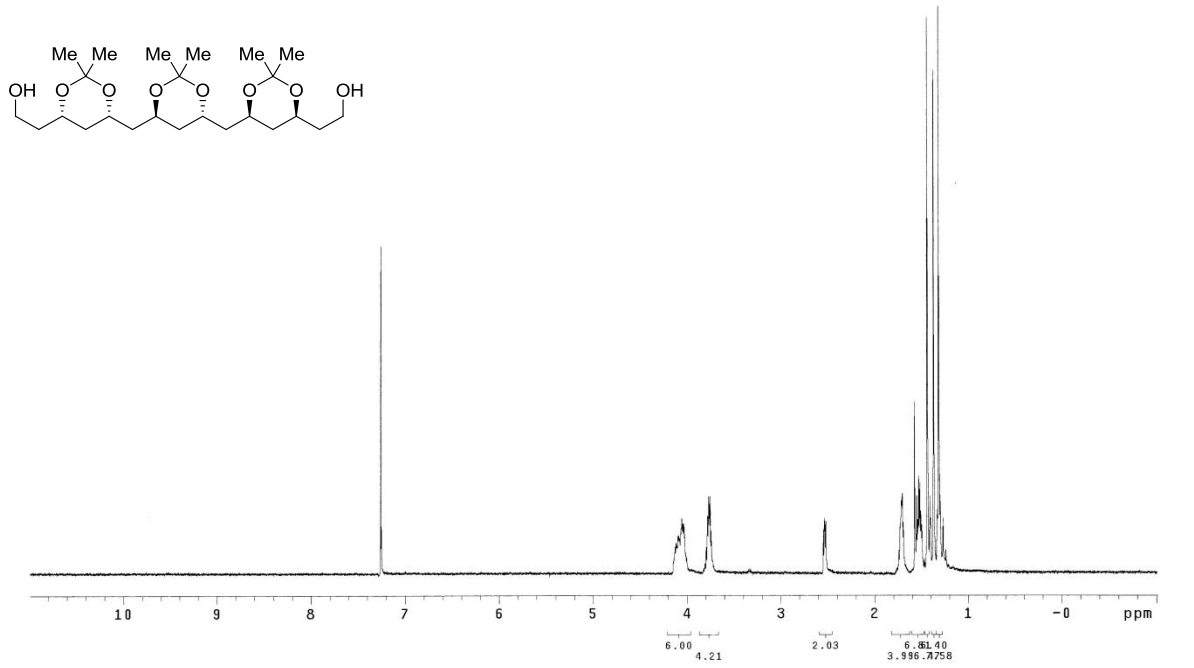


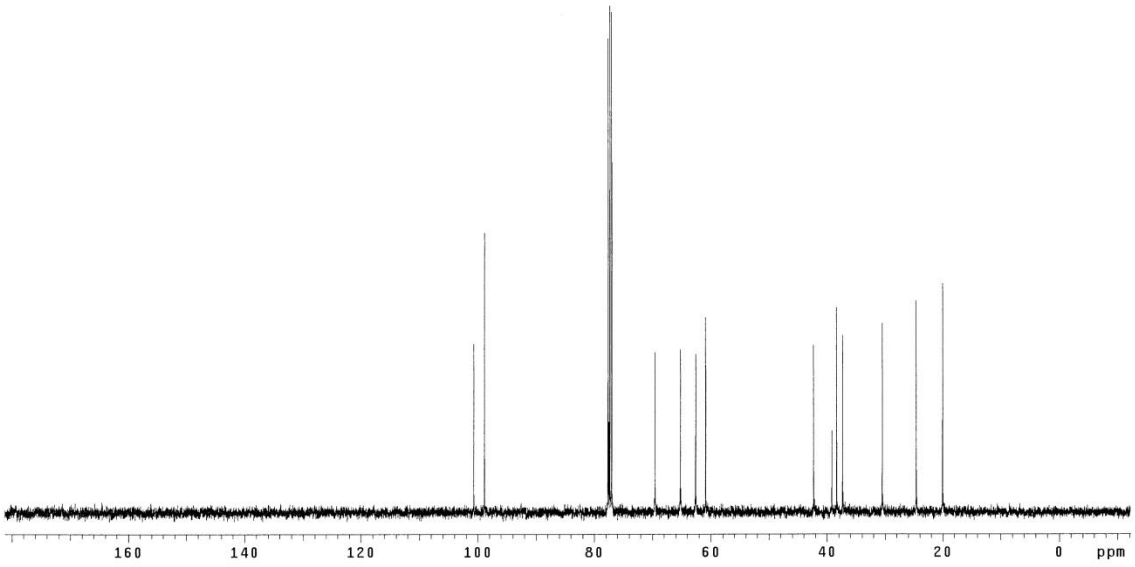
(4*S*,4'*S*,6*S*,6'*S*)-6,6'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(methylene)bis(4-allyl-2,2-dimethyl-1,3-dioxane) (5.39)



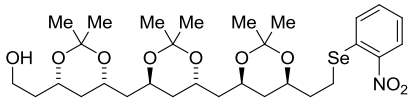


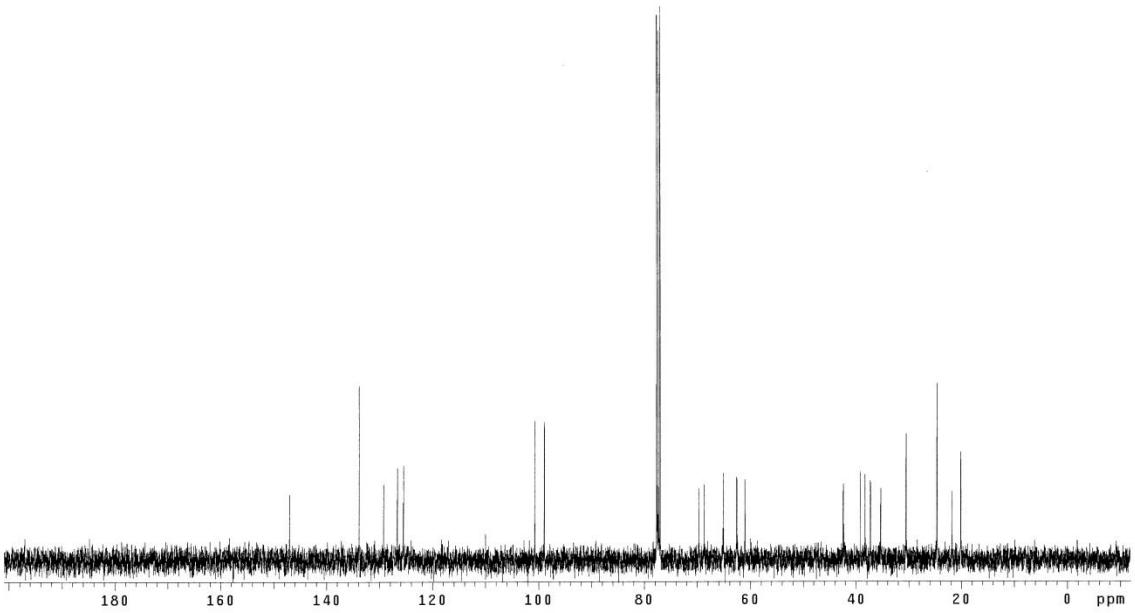
2,2'-(4*S*,4'*S*,6*S*,6'*S*)-6,6'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(methylene)bis(2,2-dimethyl-1,3-dioxane-6,4-diyl)diethanol (5.3)



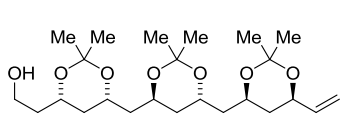


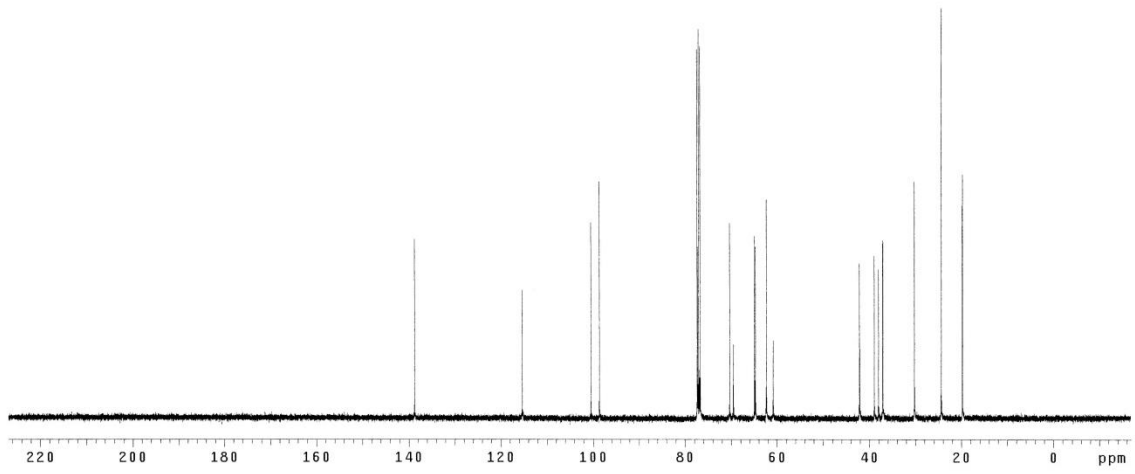
2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-(2-(2-nitrophenylselanyl)ethyl)-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (5.40)





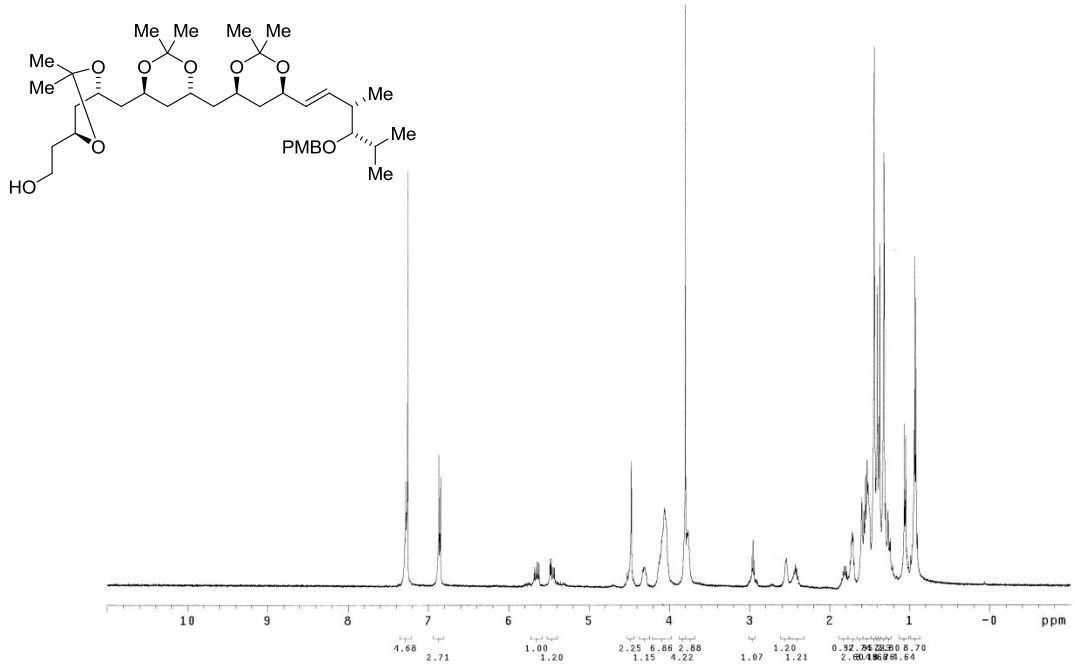
2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-vinyl-1,3-dioxan-4-yl)methyl)-2,2 dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (C)

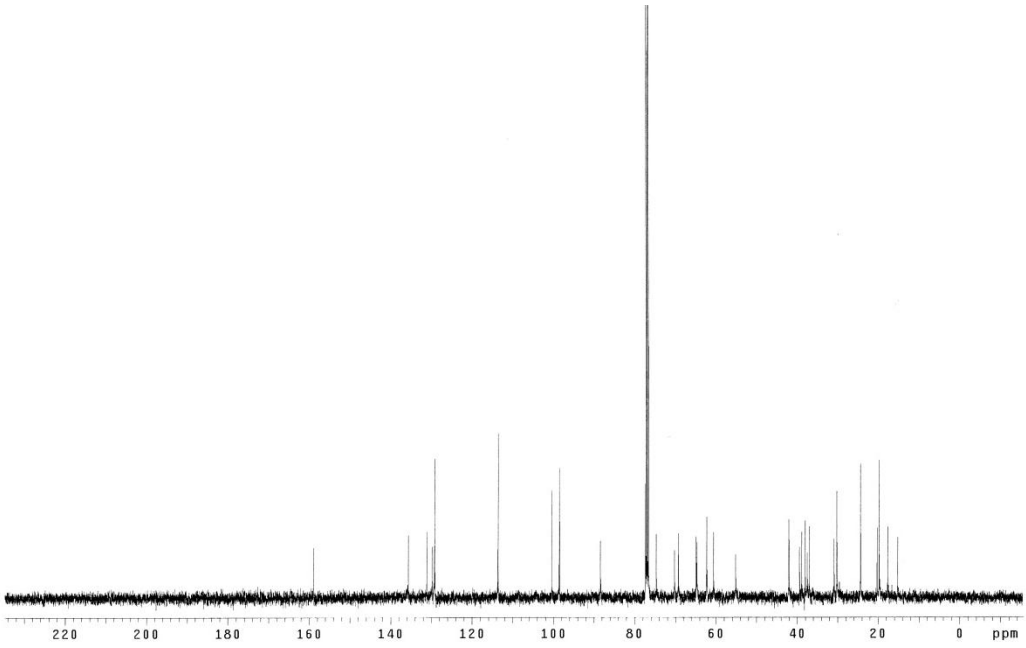




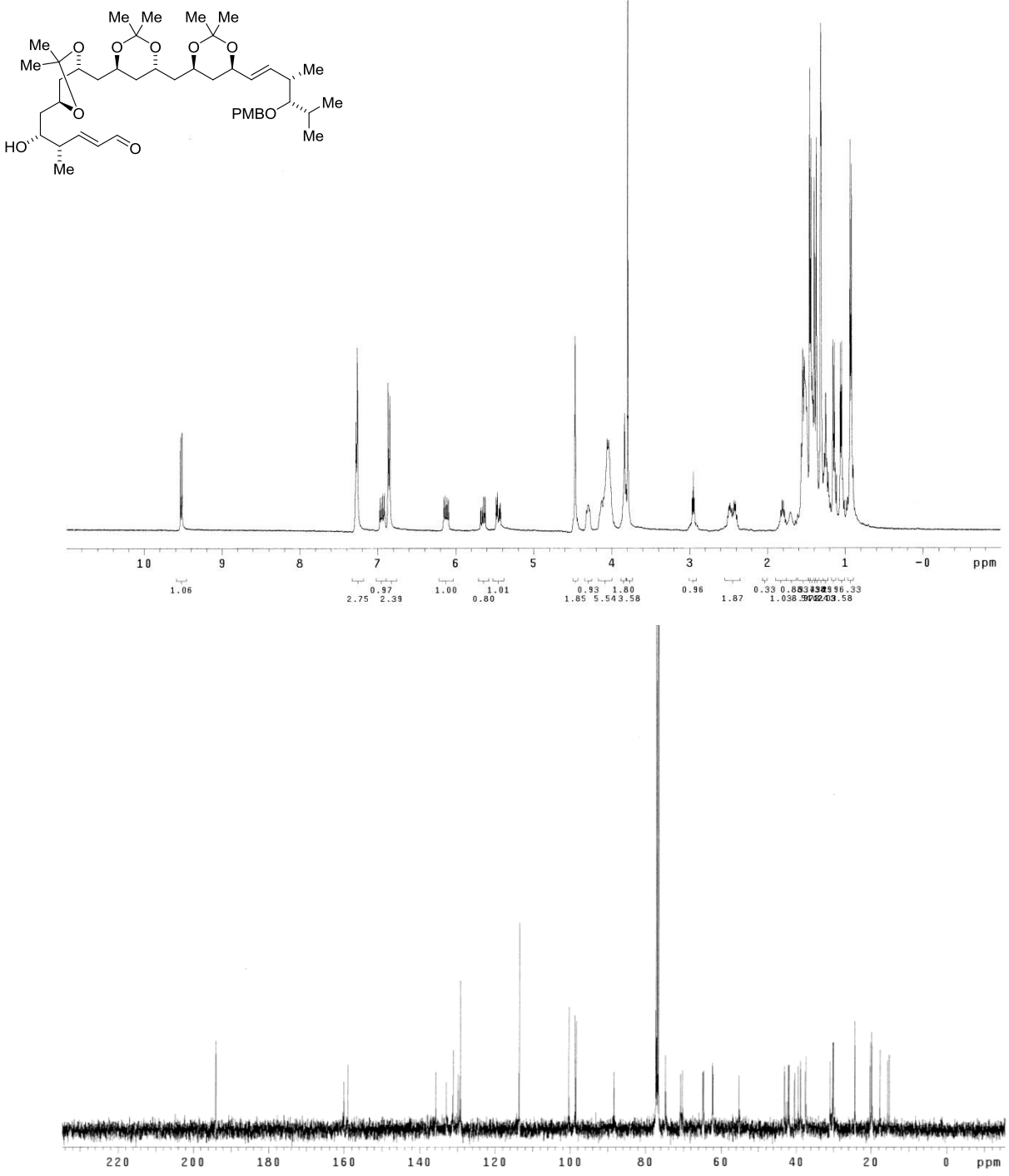
IV End Game:

2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (5.41)

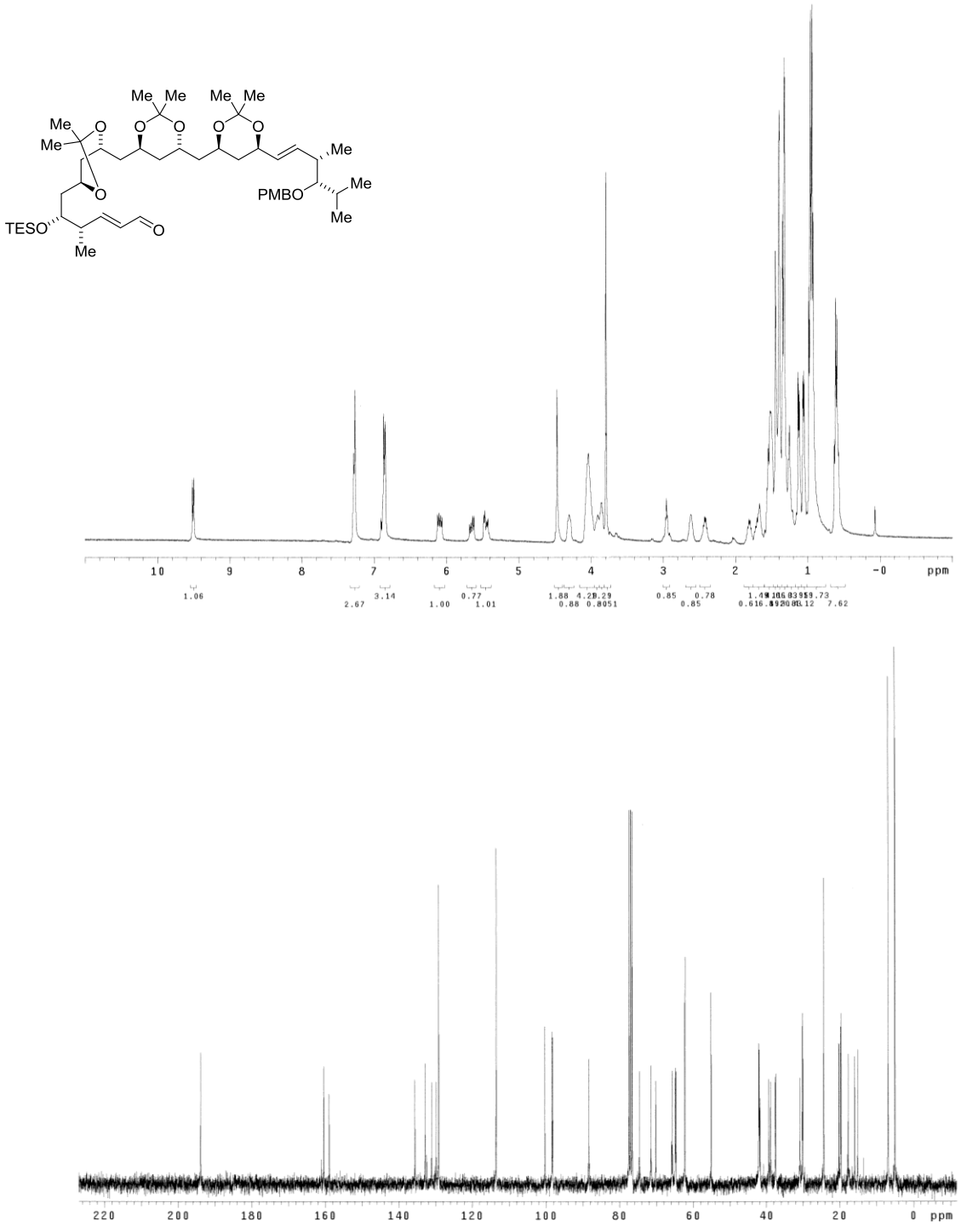




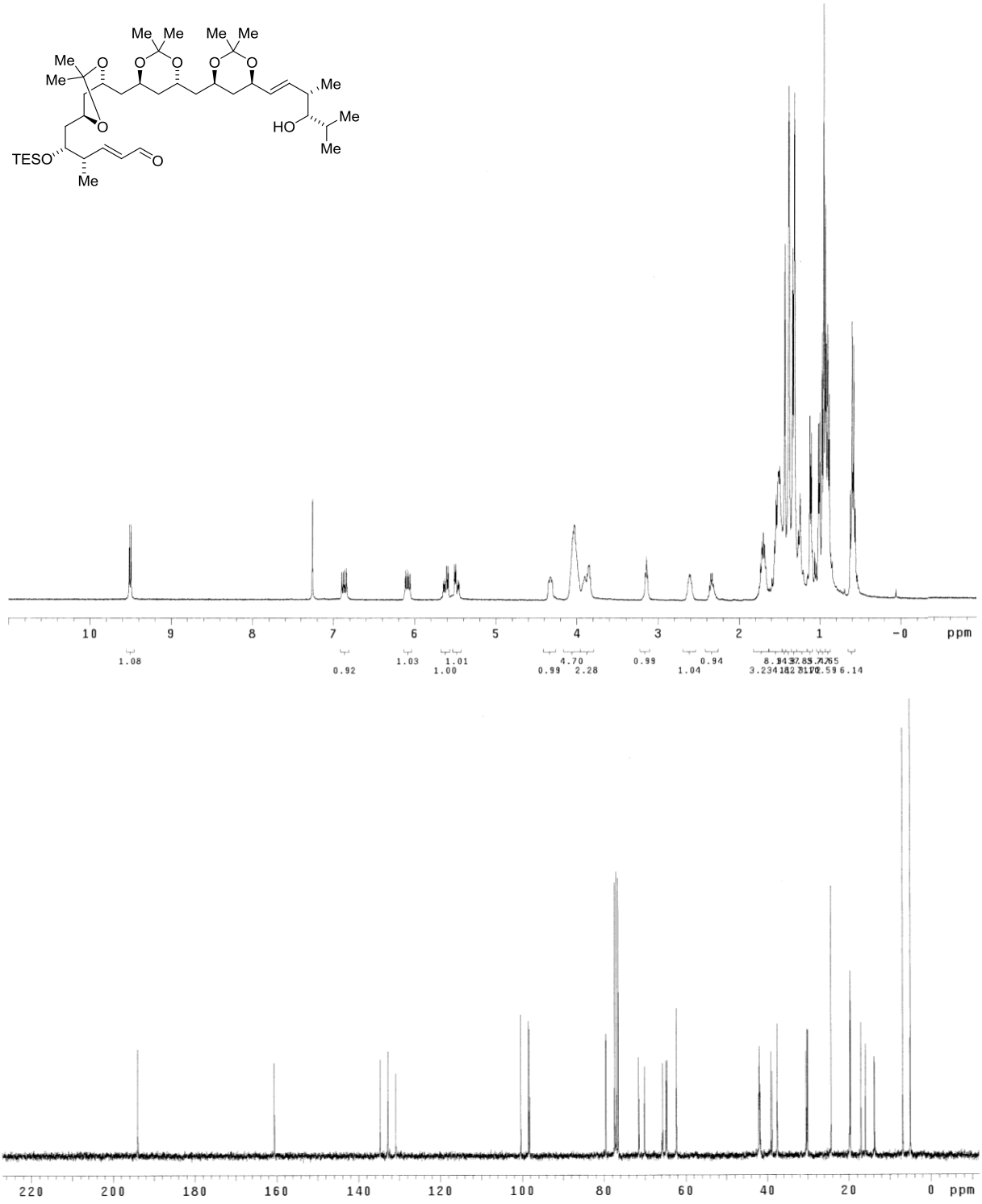
(2*R*,3*S*)-1-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-methylpent-4-en-2-ol (5.42)



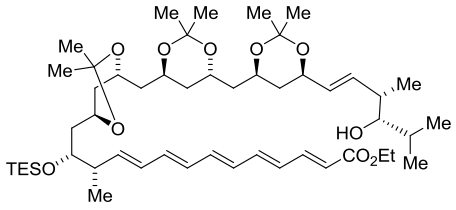
(4*S*,5*R*,*E*)-5-hydroxy-6-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methylhex-2-enal (5.43)

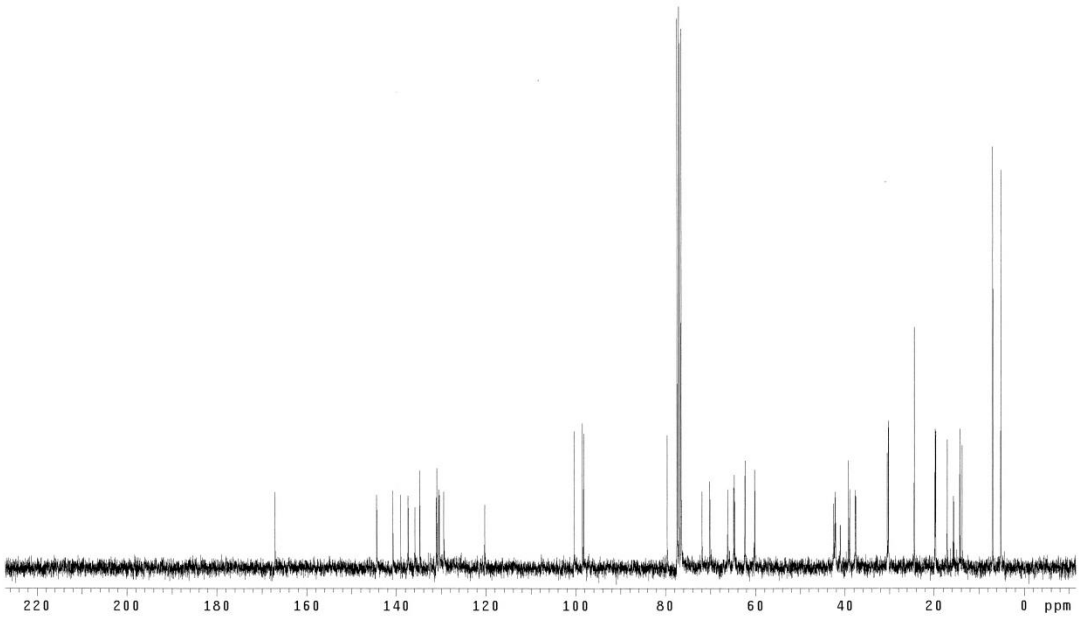


(4*S*,5*R*,*E*)-6-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-hydroxy-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methyl-5-(triethylsilyloxy)hex-2-enal (5.44)



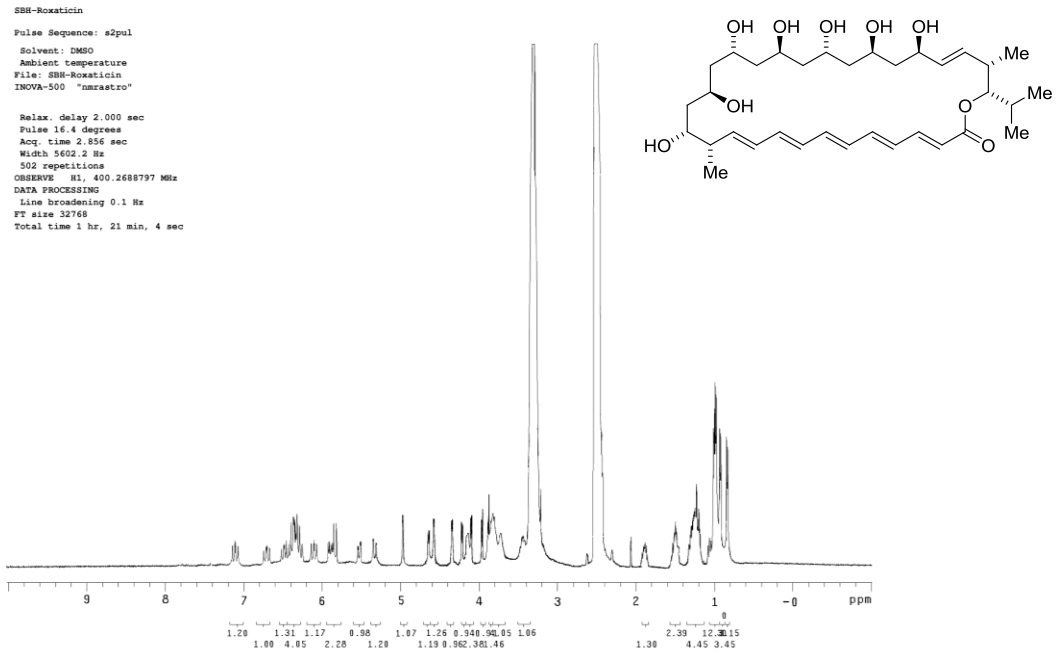
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*)-ethyl 14-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-hydroxy-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-12-methyl-13-(triethylsilyloxy)tetradeca-2,4,6,8,10-pentaenoate (5.45)

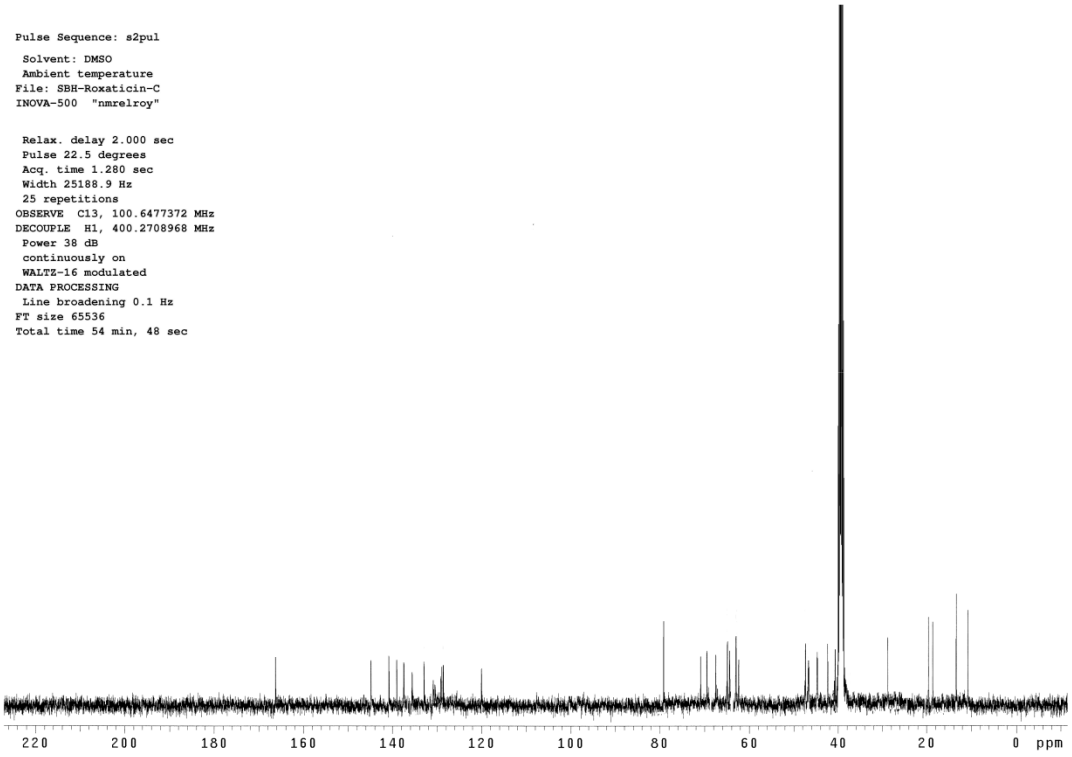




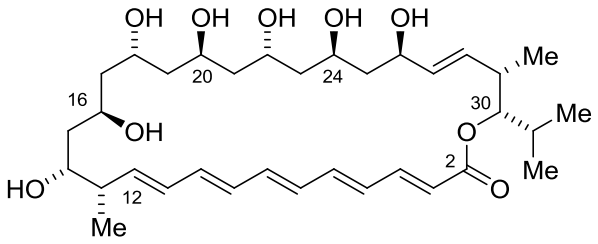
(3*E*,5*E*,7*E*,9*E*,11*E*,13*S*,14*R*,16*R*,18*R*,20*S*,22*S*,24*R*,26*R*,27*E*,29*S*,30*S*)-14,16,18,20,22,24,26-heptahydroxy-30-isopropyl-13,29-dimethyloxacyclotriaconta-3,5,7,9,11,27-hexaen-2-one

(+)-Roxaticin





IV. ^{1}H NMR Comparison for Roxaticin (d_6-DMSO)



	Natural Roxaticin[6]	Krische	Rychnovsky	Mori	Evans
Me2CH	0.84 (d, 6.5)	0.84 (d, 6.6)	0.83 (d, 6.1)	0.84 (d, 6.6)	0.84 (d, 6.6)
Me2CH	0.93 (d, 6.5)	0.92 (d, 6.6)	0.92 (d, 7.3)	0.93 (d, 6.6)	0.92 (d, 7.0)
C13-**Me**	0.99 (d, 6.5)	0.98 (d, 6.6)	0.97 (d, 7.3)	0.99 (d, 6.7)	0.97 (d, 6.6)
C29-**Me**	1.01 (d, 7.5)	1.00 (d, 6.9)	1.00 (d, 6.1)	1.01 (d, 6.8)	1.00 (d, 7.0)
H15,17,19,21,23,25	0.95-1.34, 1.16-1.34, 1.49 (m)	0.99-1.40, 1.48 (m)	1.00-1.30 (m), 1.49 (m)	1.00-1.40, 1.49 (m)	0.99-1.32, 1.48 (m)
Me2C***H***	1.87 (m)	1.86 (m)	1.86 (m)	1.87 (m)	1.86 (m)
H13,29	2.55 (m)	2.55 (m)	2.55 (m)	2.55 (m)	2.55 (m)
H14,16,18,20,22,24	3.42, 3.71-3.89 (m)	3.42, 3.72-3.98 (m)	3.42, 3.73 (s)	3.42, 3.71-3.98 (m)	3.42, 3.83 (m)
CH***OH***	3.88 (d, 6.0)	3.84 (m)	3.83 (m)	3.87 (d, 4.6)	3.83 (m)
CH***OH***	3.94 (d, 6.0)	3.93 (d, 5.8)	3.93 (d, 6.1)	3.93 (d, 5.6)	3.93 (d, 5.9)
CH***OH***	4.13 (d, 6.0)	4.12 (d, 5.0)	4.11 (d, 4.9)	4.12 (d, 5.1)	4.11 (d, 4.4)
H26	4.16 (m)	4.15 (m)	4.15 (m)	4.15 (m)	4.15 (m)
CH***OH***	4.22 (d, 5.0)	4.20 (d, 5.4)	4.20 (d, 4.9)	4.21 (d, 5.4)	4.20 (d, 5.9)
CH***OH***	4.38 (d, 4.5)	4.36 (d, 4.0)	4.35 (d, 3.7)	4.36 (d, 3.9)	4.36 (d, 4.4)
CH***OH***	4.60 (d, 4.0)	4.59 (d, 3.6)	4.58 (d, 3.7)	4.59 (d, 2.9)	4.59 (d, 3.7)
H30	4.66 (dd, 7.0, 2.5)	4.65 (dd, 7.2, 2.5)	4.64 (d, 7.3)	4.66 (dd, 9.5, 2.5)	4.64 (dd, 7.0, 2.6)
CH***OH***	5.00 (d, 2.5)	5.01 (s)	4.98 (s)	4.99 (s)	4.99 (s)
H28	5.35 (dd, 15.5, 3.0)	5.34 (dd, 16.0, 3.6)	5.34 (d, 15.9)	5.35 (dd, 16.4, 3.6)	5.33 (dd, 15.8, 3.3)
H27	5.55 (dd, 15.5, 4.4)	5.54 (dd, 15.6, 5.1)	5.50 (dd, 15.9, 3.7)	5.55 (dd, 15.4, 5.1)	5.53 (dd, 15.5, 5.0)
H3	5.83 (d, 15.5)	5.82 (d, 15.2)	5.81 (d, 14.6)	5.83 (d, 15.1)	5.82 (d, 15.0)
H12	5.89 (dd, 15.5, 7.0)	5.88 (dd, 15.6, 7.2)	5.87 (dd, 14.6, 6.1)	5.89 (dd, 15.1, 7.3)	5.89 (dd, 15.1, 7.0)
H11	6.12 (dd, 15.5, 10.0)	6.10 (dd, 15.2, 10.0)	6.10 (dd, 14.6, 11.0)	6.12 (dd, 15.4, 10.7)	6.10 (dd, 14.4, 11.2)
H9	6.28 (dd, 15.5, 10.0)	6.26-6.42 (m)	6.25-6.41 (m)	6.25-6.43 (m)	6.26-6.41 (m)
H7	6.33 (dd, 14.5, 10.0)	6.26-6.42 (m)	6.25-6.41 (m)	6.25-6.43 (m)	6.26-6.41 (m)
H10	6.36 (dd, 15.0, 10.0)	6.26-6.42 (m)	6.25-6.41 (m)	6.25-6.43 (m)	6.26-6.41 (m)
H5	6.40 (dd, 15.0, 11.0)	6.26-6.42 (m)	6.25-6.41 (m)	6.25-6.43 (m)	6.26-6.41 (m)
H8	6.48 (dd, 14.5, 10.0)	6.47 (dd, 14.4, 11.2)	6.47 (dd, 14.6, 11.0)	6.48 (dd, 15.1, 10.7)	6.47 (dd, 14.4, 11.2)
H6	6.70 (dd, 15.0, 10.0)	6.69 (dd, 15.2, 10.8)	6.69 (dd, 14.6, 11.0)	6.70 (dd, 14.4, 11.2)	6.70 (dd, 14.4, 11.2)
H4	7.13 (dd, 15.5, 11.0)	7.11 (dd, 15.6, 11.6)	7.11 (dd, 15.9, 12.2)	7.12 (dd, 15.4, 11.7)	7.11 (dd, 15.5, 11.7)

Appendix II: List of Scientific Publications

1. "Unlocking Hydrogenation for C-C Bond Formation: A Brief Overview of Enantioselective Methods"

   Hassan, A.; Krische, M. J. *Org. Process Res. Dev.* **2011,** *15,* 1236.

2. "Catalytic Enantioselective Grignard Nozaki-Hiyama Methallylation from the Alcohol Oxidation Level: Chloride Compensates for π-Complex Instability"

   Hassan, A.; Townsend, I. A.; Krische, M. J. *Chem. Commun.* **2011,** *47,* 10028.

   Highlighted in *Synfacts* **2011**, 1206.

3. "Enantioselective Vinylogous Aldol-Reformatsky Addition from the Alcohol or Aldehyde Oxidation Level *via* Iridium Catalyzed Transfer Hydrogenation: Linear Regioselectivity by Way of *C*-Bound Iridium Enolates"

   Hassan, A.; Zbieg, J. R.; Krische, M. J. *Angew. Chem. Int. Ed.* **2011**, *50,* 3493.

   Highlighted in *Synfacts* **2011**, 741.

4. "Total Synthesis of (+)-Roxaticin: A Departure from Stoichiometric Chiral Reagents, Auxiliaries and Premetallated Nucleophiles in Polyketide Construction"

   Han, S. B.; **Hassan, A.**; Kim, I.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2010,** *132*, 15559.

   Highlighted in *Synfacts* **2011**, 121.

5. "Elongation of 1,3-Polyols via Iterative Catalyst-Directed Carbonyl Allylation from the Alcohol Oxidation Level"

   Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112.

6. “1,n-Glycols as Dialdehyde Equivalent in Iridium Catalyzed Enantioselective Carbonyl Allylation form the Alcohol Oxidation Level and Iterative Two-Directional Assembly of 1,3-Polyols”

   Lu, Y.; Kim, I.-S.; **Hassan, A.**; Del Valle, D. J.; Krische, M. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5018.

   Highlighted in *Synfacts* **2009**, 997.

7. “Diastereo- and Enantioselective Reductive Aldol Addition of Vinyl Ketones via Catalytic Hydrogenation”

   Han, S. B.; **Hassan, A.**; Krische, M. J. *Synthesis* **2008**, 2669.

8. “Diastereo- and Enantioselective Hydrogenative Aldol Coupling of Vinyl Ketones: Design of an Effective Monodentate TADDOL-Like Phosphonite Ligand”

   Bee C.; Han, S. B.; **Hassan, A.**; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746.

   Highlighted in *Synfacts* **2008**, 596.

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